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Volume 232 MAY 31, 1945 Number 22

LIGATION OF THE INFERIOR VENA CAVA IN THE PREVENTION AND TREATMENT OF PULMONARY EMBOLISM*

E. Everett O'Neil, M.D.†

BOSTON

THE interruption of deep venous pathways in the treatment and prevention of pulmonary embolism has come to be a generally accepted surgical procedure. The preferred sites for division when deep venous thrombosis is present, or when pulmonary infarction has taken place without evident thrombosis but the latter is suspected, have been the superficial femoral veins, the common femoral veins and, in a few cases, the external and common iliac veins. In the majority of cases, section of the above-named vessels has been adequate to prevent further extension of thrombosis, with its possible detachment of a fatal or near-fatal embolus. It must, however, be pointed out that there have been occasions when embolism, in a few cases with a fatal result, has occurred after bilateral division of deep veins. The reasons for such fatalities are not always clear. If one has interrupted a vein at a point where a thrombus was present and is not sure that all clot had been suctioned from the proximal segment, it may well be argued that a possible remaining thrombus can produce a fatal outcome; or if the superficial, and not the common, femoral vessels have been interrupted, one may deduce that a propagating thrombus may develop in the deep femoral vein, with subsequent detachment of a fatal embolus. When, however, the first sign of trouble is a sudden pulmonary episode of mild pleuritic pain, with cough and bloody sputum, suggesting a minor embolic process, and inspection of the lower extremities reveals no evidence of the usual stigmas of deep thrombosis, one may postulate a quiet thrombosis in the deep venous plexus of the legs and feel justified in performing a bilateral division of the femoral veins. Operation may reveal no clot in either vein, and a proper division may be done. Despite this procedure a fatal embolism may occur several hours or days later. The obvious query concerns the source of this embolus, and the method of averting it. It is the purpose of this paper to suggest that, in certain selected cases, it may be pertinent to interrupt the inferior vena cava to circumvent the possibility of just such a catastrophe as has been mentioned. It must be admitted that the indications for the employment of such a procedure are limited; nevertheless, they are extremely important.

There appear to be two distinct indications for ligation of the inferior vena cava that have been encountered in a large series of divisions of deep veins; the first exists when the diagnosis of phlebothrombosis is obvious and the site of the lesion is apparent; the second exists when one or more emboli have occurred but their source is obscure. To elaborate further, in the first type of case a synchronous propagating thrombosis may take place in both legs, and when the condition is first observed the thrombotic processes may have extended to the inguinal ligaments or beyond, with or without the production of pulmonary embolism. As a more frequent finding, instead of simultaneous thrombosis in both lower extremities, a phlebothrombosis may occur in one limb, extending to the groin, the thrombus changing in character with the passage of time from a loose, nonadherent clot to a fairly solid mass that partially occludes the main vein. Within a few days the opposite leg may be affected by a typical phlebothrombosis involving the lower leg and thigh, clearly indicating operative interference. The question naturally arises, At what level should the vein be severed? Shall one perform a routine bilateral femoral division and attempt suctioning out the thrombi from the proximal portions of the veins, with the possible danger of leaving in some clot or dislodging it in the process of suctioning? Shall one divide the external or common iliac vein on one side and the common femoral vein on the other? The simplest solution to the problem appears to be to interrupt the inferior vena cava. The following case illustrates this point quite clearly.

Case 1. M. S., a 34-year-old, married woman, had a pelvic operation performed on June 6, 1944. A moderate-sized cyst was removed from the right ovary and numerous

*Presented at the annual meeting of the New England Surgical Society, Boston, September 20, 1944.

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adhesions were freed. The patient was discharged 2 weeks after an uneventful postoperative course. Ten days later she experienced moderate pain and swelling in the left leg and thigh. She was returned to the hospital, where shortly after admission she suffered a major pulmonary embolism. This was characterized by sharp substernal pain, cyanosis, a rapid, thready pulse, expectoration of bloody sputum and fear of impending death. Examination of both lower extremities revealed signs of deep venous thrombosis, the left more advanced than the right, extending to the groins. A diagnosis of bilateral, nonobstructive venous thrombosis, probably reaching into the iliac vessels, was made.

Under ether anesthesia, the inferior vena cava was exposed through a right lumbar incision. Two heavy braided-silk ligatures were applied to the lower vena cava, care being taken to avoid the lumbar veins. No attempt was made to search for intravenous clot. The patient's condition remained poor for 48 hours, but she gradually improved and was discharged from the hospital within 10 days. When last seen 2 months after the operation, she appeared to have undergone no ill effects from interruption of the vena cava. She experienced moderate discomfort in both legs after long periods of standing. Walking did not disturb her, and she carried on her usual household duties. Objectively there was no swelling in either leg.

In the second group of cases that may call for a ligation of the inferior vena cava, the indications are not quite so well defined, particularly since the source of the embolus may be entirely unknown and no clinical evidence of thrombosis may be available. Pathological and clinical observations preponderantly favor the role played by deep venous thrombosis of the lower leg in the production of pulmonary embolism. This phlebothrombosis may be very quiet and yet lethal in its manifestations, exhibiting no evidence of its presence until death ensues. Or the first intimation that such thrombosis exists may be the familiar signs of a pulmonary infarction, — evidence sufficient perhaps to justify division of the femoral vein. But if emboli continue to recur after such an operative procedure, is it correct to assume that thrombosis in the lower leg has been the instigating factor, even though there is no subsequent clinical manifestation of thrombosis? How perplexing this problem may be is shown by the following case.

Case 2. M. O'B., a 52-year-old unmarried woman, had three minor pulmonary episodes, diagnosed as pulmonary infarctions, during a 4-week interval following the performance of a cholecystectomy. Search for a focus of thrombosis in the lower extremities was nonrevealing. A phlebogram was negative for obstruction in the deep veins of the leg. Despite all negative findings, bilateral division of the common femoral veins was done. No intravenous thrombus was discovered, and free bleeding was observed from the distal and proximal vein segments on both sides.

Two days following the operation, the patient presented a classic picture of sudden pulmonary embolism, with chest pain, marked dyspnea and cyanosis and expectoration of bloody sputum. Supportive treatment was instituted and the patient recovered. A subsequent electrocardiogram was negative. Within the following 12 days, two similar attacks, both almost lethal, occurred. Interruption of the inferior vena cava was contemplated, but the patient's condition interdicted any operative interference. She slowly responded to conservative measures and left the hospital within 4 weeks of the last attack. At no time during the hospital stay or since discharge has any clinical evidence of venous thrombosis been present in either leg.

Furthermore, there have been other cases in which repeated attacks of pulmonary embolism have occurred and no treatment except rest and sedation was instituted, yet at no time during or after these attacks has any evidence of deep thrombosis in the lower limbs been present, even though the most painstaking search, including phlebography, was carried out.

One may thus postulate a propagating thrombus arising from some other source, such as the prostatic or uterine plexus, wending its sinister way through the hypogastric vein and the common iliac vein into the inferior vena cava. Anyone who is familiar with surgery of the female pelvis is aware of the tremendous size that the veins of the uterine plexus may attain. Their engorgement during pregnancy, in the presence of pelvic disease or in the course of routine postoperative convalescence, with its attendant immobilization, creates a most favorable medium for the formation and propagation of a silent thrombus. Likewise, in the male, the prostatic plexus gives a simila picture. This plexus of veins, sometimes termed the "prostaticovesical plexus," surrounds the prostate gland and the neck of the bladder. It receives the deep dorsal vein of the penis and veins from the seminal vesicles and empties into the hypogastric vein. All these veins may enlarge to considerable dimensions and become varicosed and thrombosed. Hence, when the

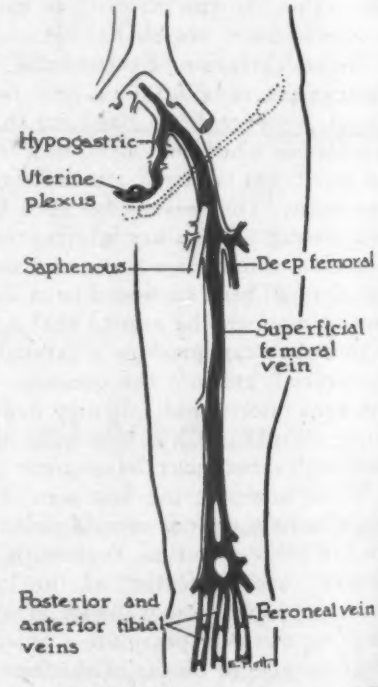

Figure 1. *Sketch Showing Origin and Cause of Deep Venous Propagating Thromboses.*

The thrombus may be initiated in the lower leg veins, or in the deep femoral system, or in the deep pelvic veins, such as the uterine or prostatic venous plexuses.

presence of so-called "silent thrombosis" is suspected the thrombotic process may well exist in one or several groups of deep veins, namely, the venous channels of the lower leg, the deep femoral veins and the venous plexuses of the pelvis (Fig. 1). When

the source of the embolus is unknown, the best guarantee of safety appears to be interruption of the inferior vena cava, such as was performed in the following case.

Case 3. L. D. O., a 65-year-old, married woman, had a cholecystectomy performed on June 13, 1944, at which time an acute gangrenous gall bladder was removed. The convalescence was essentially uneventful and afebrile until the 19th postoperative day. During the next 4 days the pulse, temperature and respirations were elevated, and signs of pulmonary infarction were found in the right chest. X-ray studies confirmed this diagnosis. A repeat chest plate taken several days later showed a much larger area of infarction than at the first observation. The clinical course and x-ray findings suggested repeated pulmonary embolisms. There was no evidence of thrombosis in either lower extremity. Because of this negative finding, interruption of the inferior vena cava was performed under Pentothal-cyclopropane anesthesia through a right lumbar incision. The postoperative course was excellent, save for one or two gastrointestinal upsets. Except for a sense of heaviness and minimal swelling in both legs when standing, the patient has no complaints.

In the above case, an equally good result might have been obtained by bilateral division of the common femoral vein, but previous experiences in which repeated embolisms have occurred after such a procedure, with the belief that a silent propagating thrombosis might exist in the pelvic vessels, influenced me in ligating the inferior vena cava.

Several considerations present themselves in a discussion of ligation of the inferior vena cava. They include the pattern of the collateral circulation that follows on such an interruption, and the operative procedure and the state of the venous return from the legs after occlusion of the vena cava.

In a recent communication, Homans[1] has demonstrated the more satisfactory collateral circulation available when the common iliac vein, rather than the common femoral vein, is divided. A further significant clinical observation is made by the same writer, to the effect that there is much less venous congestion and swelling of the extremities following such a division. It should be pointed out that a parallel situation exists when the inferior vena cava is occluded. There is equally as rich a collateral venous pattern set up after such interruption as after division of the common iliac vein. The theoretical disadvantage of the former procedure, in relation to return blood flow from the legs, is the interference with shifting of blood from one side of the pelvis to the other — a situation that does not obtain when only one common iliac vein is obstructed. This apparent disadvantage, however, is not borne out by any serious clinical aftereffects with which I am familiar.

The collateral pathways available after ligation of the lower vena cava fall roughly into three groups — the superficial, the deep, and those of the ascending lumbar trunks. The first of them comprise the superficial circumflex iliac and the superficial epigastric veins, which connect the saphenous system with the superficial thoracic vein and those of the upper abdominal wall. The deep pathways are formed by the anastomosis of the deep circumflex iliac, superior epigastric and lumbar veins, thereby connecting the external iliac veins with the internal mammary and ascending lumbar veins. The ascending lumbar trunks begin in the pelvis on either side of the promontory of the sacrum and communicate with the sacral, common iliac, hypogastric and iliolumbar veins. As they ascend they connect with the lumbar veins, the inferior vena cava and the right renal vein. The right lumbar trunk becomes the azygos vein and terminates in the superior vena cava; the left continues as the hemiazygos vein and eventually enters the right azygos vein. Figures 2, 3 and 4 — the first two taken from

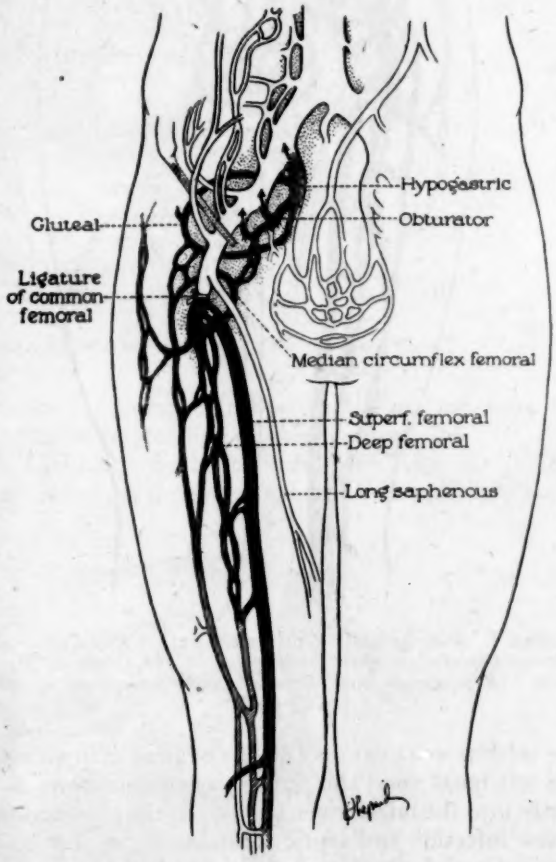

Figure 2. *Diagrammatic Representation of the Venous Return and Collateral Blood Supply following Division of the Common Femoral Vein. (Reproduced from Homans[1] with permission of the publisher.)*

the description by Homans — portray the essential differences in the collateral channels at various levels of interruption of deep veins.

Technically, the exposure and ligation of the lower vena cava is not so hazardous or so difficult as would first appear. Heretofore, the majority of ligations have been carried out as emergency procedures following operative accidents, particularly after nephrectomy. For obvious reasons, approach to the vena cava under such conditions is extremely formidable. Such a problem, of course, does not exist in an elective operation. Interruptions of the vena

cava have also been performed because of septic thrombosis in the deep pelvic veins.[2] The approach in these cases is always transperitoneal, because of the necessity of ligating the ovarian veins as well as

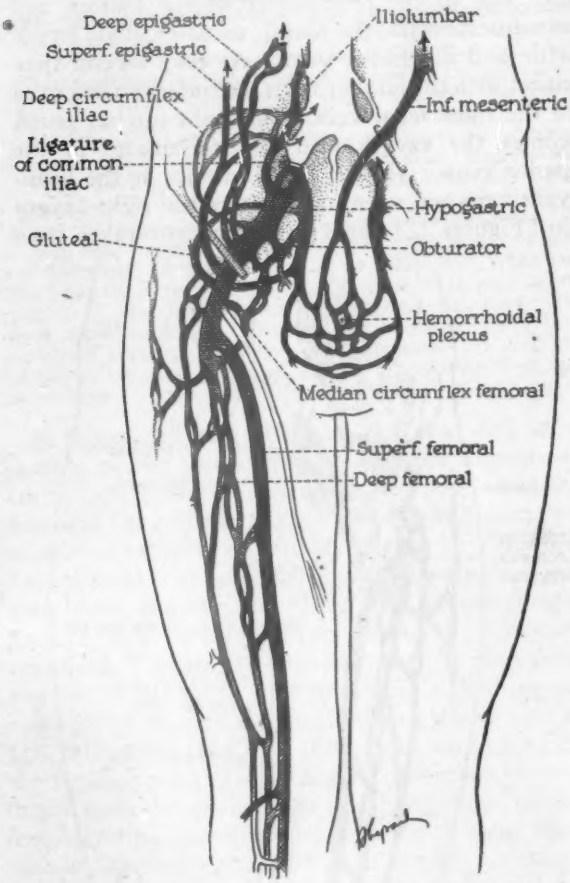

FIGURE 3. *Diagrammatic Representation of the Rich Collateral Venous Circulation after Interruption of the Common Iliac Vein. (Reproduced from Homans[1] with permission of the publisher.)*

the inferior vena cava. The left ovarian vein enters the left renal vein; the right ovarian vein flows directly into the inferior vena cava. In the presence of pelvic infection and septic thrombosis, possible dissemination of septic emboli by way of the blood stream into the kidneys and lungs demands the division of these vessels. In aseptic thrombosis or phlebothrombosis, this indication does not obtain. The ovarian veins are small, and very likely do not dilate enough to harbor a propagating thrombus of sufficient size to produce a major embolism. The approach to the inferior vena cava may therefore be entirely extraperitoneal.

One of two incisions may be employed. The first (Fig. 5) is that customarily used in exposing the right iliac vessels, and is made approximately parallel to the inguinal ligament extending laterally toward the flank. After retraction of the peritoneum mesially, the right common iliac vein is clearly brought into view; further retraction upward and inward discloses the lower inferior vena cava. The alternate incision (Fig. 6) is placed higher up in the flank. It is the approach usually employed in the operation of lumbar sympathectomy. It gives ready access to the vena cava, and appears to be the preferable route. If troublesome bleeding is encountered, the better exposure rendered by the lumbar incision makes control of such a complication less difficult. Also, little manipulation is required in tying off the vena cava through this incision, a consideration if much thrombus is present in the iliac vessels. Actual ligation of the vena cava is done with two heavy braided-silk ligatures placed about the vessel 2 or 3 cm. apart. Caution should be used when placing these ligatures in the region of the lumbar veins. These veins, four in number, on either side of the lower vena cava may easily be injured in the maneuver of sliding the ties under the main venous trunk. It is necessary neither to open nor to divide the inferior vena

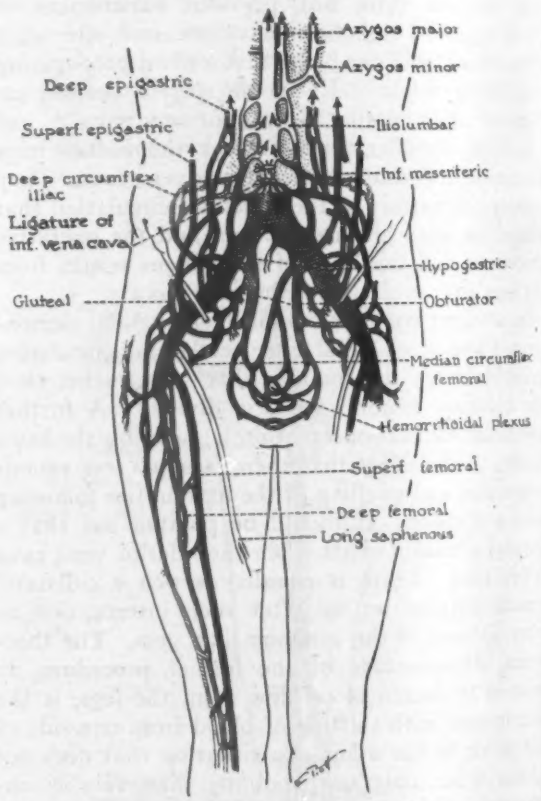

FIGURE 4. *Diagrammatic Sketch Illustrating the Abundant Collateral Venous Supply following Ligation of the Inferior Vena Cava.*

The venous return is comparable to that obtained when a bilateral common-iliac-vein interruption is performed.

cava. If a thrombus is contained within the vessel, not enough will be detached to be dangerous. Ligation will serve the purposes of interruption equally as well as division.

The determination of venous pressures in measuring the status of venous return from the legs, follow-

ing ligation of the inferior vena cava, is probably of considerable value. It is apparent that venous pressure is considerably raised following occlusion of a rapidly after interruption of the vena cava. Theoretically, in cases of advanced age with failing myocardium, caution should be used in ligating the in-

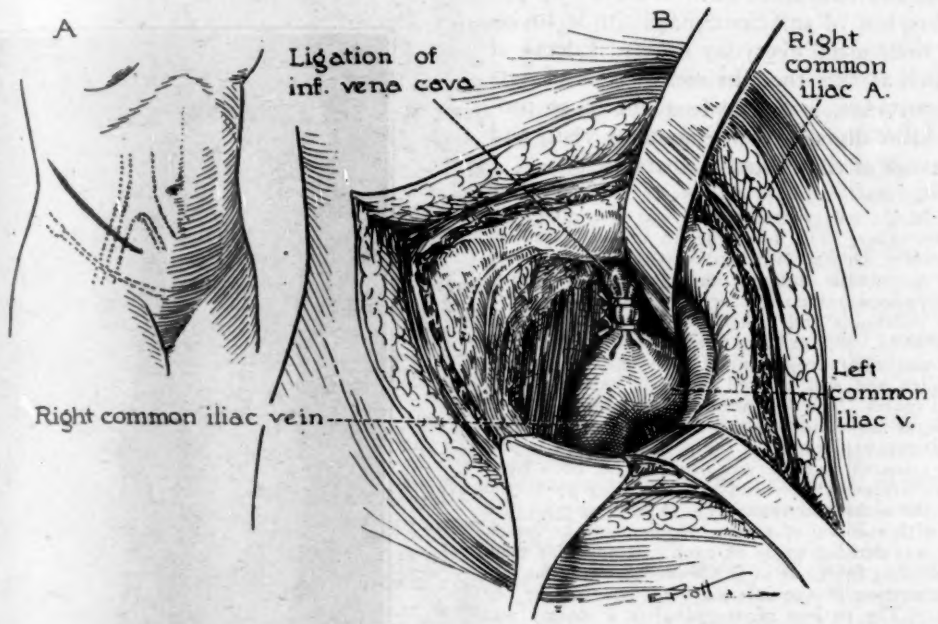

FIGURE 5. *The Abdominal Extraperitoneal Operative Approach to the Lower Inferior Vena Cava.*

main venous trunk, without, however, causing any undue effect on a normal heart muscle. If pressure in the great veins becomes excessive, the heart muscle responds by contracting more vigorously, ferior vena cava. Further studies are necessary for fuller understanding of this problem.

Clinically, both the immediate and the remote effects of caval ligation are satisfactory. Eight cases

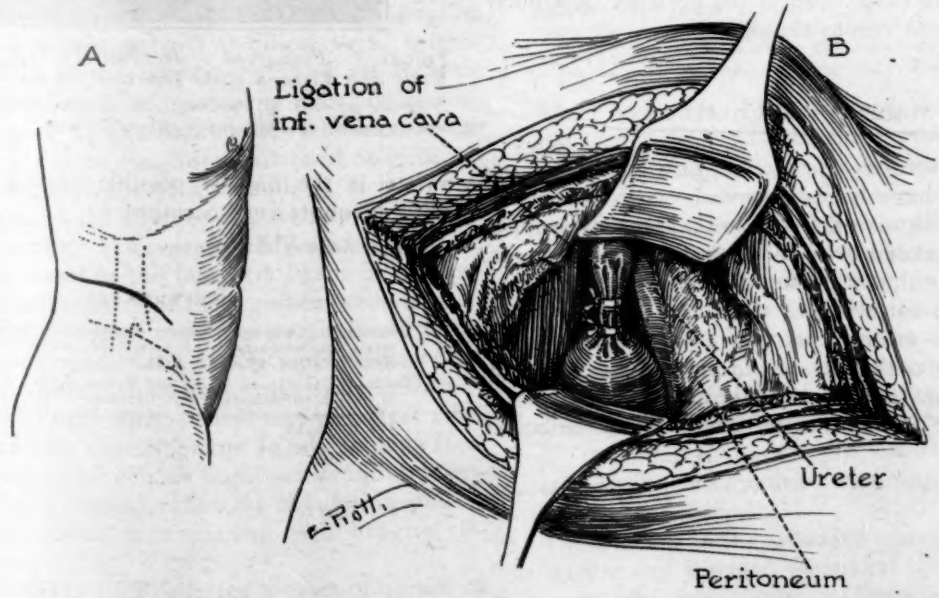

FIGURE 6. *The Lateral Extraperitoneal Operative Approach to the Inferior Vena Cava. The incision is the one customarily used in lumbar sympathectomy.*

propelling more blood into the arterial tree and thereby lowering venous pressure and maintaining it at a normal level. It is thus evident that venous pressure should return to normal quite of interruption of the inferior vena cava have been performed in this series. In 5 of these, there had been obvious thrombotic involvement of the lower extremities; in 3, pulmonary embolism had oc-

curred but no source was evident. In no case have there been any untoward postoperative effects. Minimal discomforts, such as heaviness, numbness and moderate swelling, have been observed by patients, but are not of sufficient magnitude to interfere with their usual everyday duties. Edema of the legs, which at first thought seems to be of outstanding importance, is not so frequent or so pronounced as after division of the femoral vein, and with the passage of time usually clears up.

CASE 4. J. McC., a 41-year-old man, was brought to the hospital in December, 1939, following an unusual accident 8 weeks previously. He had been struck in the backs of both knees by an automobile bumper, suffering extensive contusions and abrasions but no fractures. Considerable swelling, coldness, numbness and mottled discoloration of both lower legs followed. On examination the pedal, popliteal and femoral pulsations were absent in both legs, which were markedly swollen and still showed signs of hematomas in both popliteal spaces. The feet were cold and cyanotic, but the patient could move his toes and feet without difficulty.

A transperitoneal exploration of the pelvic vessels was performed. Extensive thrombosis was observed in both right and left common iliac arteries and veins, leading up to the bifurcation of the aorta and vena cava. A left common iliac arterectomy, with removal of a 5-cm. segment of the vessel, was done. It was decided to tie off each common iliac vein, but profuse bleeding from one of the lower lumbar veins dictated an interruption of the inferior vena cava above the bleeding point. The patient recovered after a stormy and protracted convalescence. The immediate effect on the swelling of the legs was striking. Within 48 hours the edema began to subside and did not reappear even on standing. The legs have remained free of swelling since the operation (Fig. 7).

This case illustrates the rapid collateral anastomoses that are effected after interruption of the inferior vena cava, even in the presence of a fairly well-advanced venous thrombosis.

SUMMARY AND CONCLUSIONS

Two indications for interruption of the inferior vena cava have been suggested: when concurrent phlebothrombosis exists in both lower extremities and has extended to or above the inguinal ligament; and when pulmonary embolism has occurred and its source is not evident.

In one's enthusiasm for diagnosing lower-leg thromboses as the *bête noir* in pulmonary embolism, the fact that aseptic thrombosis may exist in the large pelvic vessels and initiate a serious embolism should not be overlooked. If one is to operate on cases of deep venous thrombosis on suspicion alone, the best assurance that can be given for the patient's safety is the highest possible ligation compatible with adequate venous return.

FIGURE 7. *Photograph of the Patient's Legs (Case 4) Five Years after Ligation of the Inferior Vena Cava. Note the absence of swelling. At no time following operation was any swelling apparent in either extremity.*

270 Commonwealth Avenue

REFERENCES

1. Homans, J. Deep quiet venous thrombosis in lower limb: preferred levels for interruption of veins: iliac sector or ligation. *Surg., Gynec. & Obst.* 79:70-82, 1944.
2. Collins, C. G., Jones, J. R., and Nelson, E. W. Surgical treatment of pelvic thrombophlebitis: ligation of inferior vena cava and ovarian veins: preliminary report. *New Orleans M. & S. J.* 96: 324-329, 1943.

THE CRUVEILHIER–BAUMGARTEN SYNDROME*

Report of a Case

ALEXANDER BLAIN, III, M.D.,† AND MUIR CLAPPER, M.D.‡

DETROIT

INFREQUENTLY a venous hum or bruit occurs in the dilated collateral venous channels that may develop in portal obstruction. In 1942, Armstrong et al.[1] reviewed the 53 published cases of this phenomenon and added 2 cases of their own. Actually, 5 of the cases — including 1 of Armstrong's — showed persistence of a patent umbilical vein without portal obstruction. Since the review of Armstrong, several additional cases of portal obstruction associated with a venous hum heard over the dilated collateral veins have been reported, mainly by English and French authors.

HISTORICAL CONSIDERATIONS

Pégot[2,3] in 1833 observed a patient who had dilated veins in the abdominal wall, a caput medusae and a loud venous hum at the umbilicus. Post-mortem examination revealed a widely patent umbilical vein associated with a small liver and spleen that were grossly normal in appearance. This case was again reported in 1835 by Cruveilhier,[4] who postulated that the patient had a congenital defect of the umbilical circulation with atrophy that was probably secondary to this defect. Baumgarten[5] in 1907 reported the case of a sixteen-year-old boy who had distended abdominal veins, ascites, splenomegaly, anemia and leukopenia. Post-mortem examination revealed a widely patent umbilical vein, splenomegaly "not of the Banti type" and an atrophic liver, with subcapsular increase in interlobular connective tissue. It was Baumgarten's belief that the disease was due to congenital failure of obliteration of the umbilical vein with hypoplasia of the liver. He emphasized the absence of a well-developed cirrhosis. Sappey,[6] however, in 1859 stated that the large vein found in the falciform ligament in some cases was independent of the umbilical vein.

Thayer's[7] review of the 19 cases published up to 1911 demonstrated that a majority of the cases that presented a venous hum had good evidence of cirrhosis of the liver without a patent umbilical vein. Thayer added a case from the Johns Hopkins Hospital in which the venous hum was definitely associated with a dilated collateral circulation due to portal obstruction in a patient with hepatic cirrhosis.

Hanganutz[8] in 1922 collected 6 cases of partial or total persistence of the umbilical vein in what he termed "Cruveilhier–Baumgarten cirrhosis." Several authors subsequently published case reports under this title. Later Fiessinger and Michaux[9] analyzed the reported cases together with their own cases and concluded that Cruveilhier–Baumgarten cirrhosis was not truly a disease entity.

Armstrong et al.[1] accepted the term "Cruveilhier–Baumgarten syndrome" as applying to those cases having a clinical picture of portal obstruction featured by a loud abdominal murmur and thrill and periumbilical venous distention. After analyzing the data of the published cases, they accepted only 4 as having the true congenital abnormality that results in Cruveilhier–Baumgarten disease as originally described. They were able to add 1 case of their own from the Los Angeles County Hospital.

In differentiating the true Cruveilhier–Baumgarten disease, a very rare congenital anomaly of which only 5 well-proved examples are known, and the Cruveilhier–Baumgarten syndrome, which is usually the result of cirrhosis of the liver, Armstrong states:

> . . . any patient having portal hypertension, generally with splenomegaly, and in whom evidence in the form of visible veins, murmurs and thrill of excessively prominent umbilical circulation exists, merits the diagnosis of *Cruveilhier–Baumgarten syndrome. . . . Those cases which show at necropsy patency of the umbilical vein itself together with atrophy and little or no fibrosis of the liver would then be considered as examples of Cruveilhier–Baumgarten disease.*

Lutembacher[10] in 1936 reviewed the subject of the genesis of the venous hums and proved that they arise from veins, being most intense at the point where a small vein enters a dilated vein. The bruits have most often been heard either in the epigastrium over the course of the falciform ligament (containing dilated periumbilical veins) or over dilated superficial veins. They have also been heard in the splenic area, over dilated coronary veins and over the liver. The murmurs heard in the Cruveilhier–Baumgarten syndrome have been described as "the roaring of a wind through a cave or humming of a top" (Gambarati, quoted by Thayer[7]) and, in 1 case (Catti[11]), as "a musical ringing sound like that of an Aeolian harp."

The murmur in the following case was continuous in nature and sounded somewhat like a hurricane. It was best heard over a prominent superficial varicosity near the umbilicus.

CASE REPORT

A. M., a 46-year-old man of Rumanian birth, was admitted to the Detroit Receiving Hospital on March 23, 1944, complaining of swollen legs and a distended abdomen of 8 months'

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duration. The past history revealed chronic alcoholism of long standing. He had been imbibing three or four bottles of beer and several drinks of whisky daily since the age of 14. It is of unusual interest that the abdomen had been tapped for ascites 23 years previous to the present illness after a progressive enlargement of 3 months' duration. Four thousand cubic centimeters of fluid was removed. Following the paracentesis there was no abdominal distention until the onset of the present illness. In July, 1943, the patient noticed a slight swelling near the umbilicus, just under the skin and easily reducible with a finger. This mass was "blue" (apparently a vein) and marked the onset of a gradual and generalized enlargement of the abdomen that progressed until the time of admission. The abdominal swelling was painless until 1 month prior to admission. Edema of the ankles had been present for 5 months. There was no cough, dyspnea, palpitation, hematemesis, tarry or bloody stools or the like. A thorough dietary history revealed no specific nutritional deficiency but rather a generally poor food intake.

Physical examination revealed a well-developed, slightly icteric man with a markedly distended abdomen and pitting edema of the ankles. Over the tense abdominal surface were many large dilated veins that filled from below upward. These veins fused about the umbilicus to form a classic caput medusae (Fig. 1). Numerous spider angiomas were present over the shoulders, back and abdomen. The tongue was smooth and of a striking magenta color. The head and neck were otherwise normal. Examination of the chest revealed a few moist crackling rales at the lung bases. The heart was slightly enlarged to the left, and there was a soft blowing systolic murmur at the apex. Abdominal examination revealed shifting dullness and a fluid wave. A continuous thrill was easily palpated over the large dilated vein just above and to the right of the umbilicus (Fig. 2). Auscultation in this area revealed a continuous murmur that was extremely loud but varied in intensity ("like a hurricane"). Pressure on the vein below this dilatation obliterated the venous hum and thrill. The scrotum and the lower extremities from the hips down exhibited marked pitting edema.

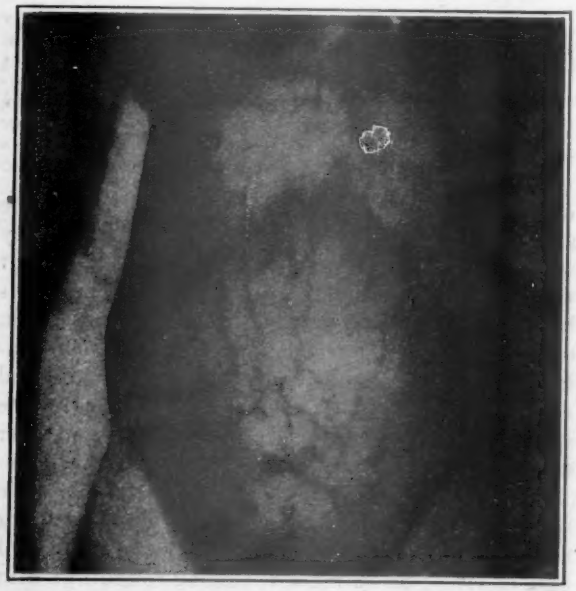

FIGURE 1. *Infrared Photograph Showing the Caput Medusae.*

The liver and spleen could not be palpated. The rectal and neurologic examinations revealed nothing significant.

The serum albumin level was persistently low, varying from 1.6 to 2.6 gm. per 100 cc. in six determinations. The lowest serum globulin level was 4.2 gm. per 100 cc., and the highest 4.7 gm. The amount of urobilinogen in the urine on repeated examination was markedly increased as measured by a rough dilution method, positive tests being obtained on urine diluted as much as 1:400. After the oral administration of 6 gm. of sodium benzoate in the performance of the hippuric acid test, an amount of hippuric acid equivalent to 1 gm. of benzoic acid was excreted in a 4-hour urine specimen. Repeated icterus indices varied from 10 to 50 units.

FIGURE 2. *Photograph Showing the Varicosity near the Umbilicus over Which the Intensity of the Venous Hum Was Greatest.*

The van den Bergh reaction was direct, immediate and positive. The serum bilirubin was 0.9 mg. per 100 cc. Hematologic studies revealed a hemoglobin of 11 gm. per 100 cc. and a red-cell count of 3,810,000. This gave a color index of 1.01. The white-cell count was 9950, with 82 per cent neutrophils (68 per cent filamented), 9 per cent lymphocytes, 7 per cent eosinophils and 2 per cent monocytes. The neutrophils contained toxic granulations. The platelet count was 297,000. The bleeding time was 2.5 minutes, the coagulation time 2.5 minutes, and the prothrombin 78 per cent of normal. Clot retraction began in 45 minutes and was complete in 4 hours.

Urinalyses were persistently negative. Repeated stool examinations were benzidine-positive and contained bile. Over 1000 cc. of ascitic fluid was aspirated in each of three paracenteses. This fluid was negative for neoplastic cells, blood and tubercle bacilli. Its specific gravity of 1.016, and an albumin content of 8.4 gm. per 1000 cc. showed it to be a transudate.

An electrocardiogram revealed a sinus tachycardia and evidence of myocardial damage — early left ventricular in type. A stethogram recording made simultaneously with the electrocardiographic tracing showed a continuous murmur the intensity of which was greatest at the umbilicus. A chest x-ray film showed elevation of both leaves of the diaphragm due to the abdominal distention by fluid. Above the diaphragm there were patchy areas of atelectasis at both lung bases. The venous pressure in the right antecubital vein was equivalent to that of 6 cm. of saline solution, as contrasted with a venous pressure of 17 cm. in a dilated superficial vein near the site of origin of the venous hum.

On April 18, the patient suddenly became drowsy and lapsed into coma. He vomited and developed Kussmaul breathing, and died on the following day.

Unfortunately, permission for autopsy could not be obtained.

This patient's long history of chronic alcoholism, together with the hypoproteinemia, icterus, abnormal benzoic acid excretion, urinary urobilinogen and the findings of portal obstruction, established the diagnosis of cirrhosis of the liver. The demon-

stration of a venous hum in association with proved cirrhosis of the liver suggests strongly that this case is an example of the Cruveilhier–Baumgarten syndrome rather than Cruveilhier–Baumgarten disease, in which the venous hum is due to a persistence of a patent umbilical vein. In the absence of post-mortem examination we cannot be absolutely certain that a patent umbilical vein was not also present, but the rarity of this anomaly makes this possibility quite unlikely.

Summary

A case of hepatic cirrhosis presenting the features of the Cruveilhier–Baumgarten syndrome is reported. A brief history of this syndrome and its relation to the extremely rare congenital Cruveilhier–Baumgarten disease are discussed.

References

1. Armstrong, E. L., Adams, W. L., Tragerman, L. J., and Townsend, E. W. Cruveilhier–Baumgarten syndrome: review of literature and report of 2 additional cases. *Ann. Int. Med.* **16**:113-151, 1942.
2. Pégot. Anomalie veineuse. *Bull. Soc. anat. de Paris* **7**:108, 1833.
3. *Idem.* Tumeur variqueuse, avec anomalie du système veineux et persistence de la veine ombilicale, dévellopement des veines sous-cutanées abdominales. *Bull. Soc. anat. de Paris* **8**:49-57, 1833.
4. Cruveilhier, J. Maladies des veines. Part 16. In *Anatomie pathologique du corps humain.* Vol. 1. Paris: J. B. Baillière, 1829–35.
5. Von Baumgarten, P. Ueber vollständiges Offenbleiben der Vena umbilicalis; zugleich ein Beitrag zur Frage des Morbus Bantii. Arb. a. d. Geb. d. path. Anat. . . . Inst. zu Tübing **6**:93-110, 1907.
6. Sappey, C Recherches sur quelques veines portes accessoires. *Compt. rend. Soc. de biol.* Third series. I (pt. 2): 3-13, 1859.
7. Thayer, W. S. Of presence of venous hum in epigastrium in cirrhosis of liver. *Am. J. M. Sc.* **141**:313-327, 1911.
8. Hanganutz, M. Sur la cirrhose de Cruveilhier–Baumgarten. *Presse méd.* **30**:732-734, 1922.
9. Fiessinger, N., and Michaux, L. A propos de la cirrhose de Cruveilhier–Baumgarten: deux cas nouveaux. *Bull. et mém. Soc. méd. d. hop. de Paris* **54**:88-92, 1930.
10. Lutembacher, R. Bruits de souffle veineux et cirrhose de Laennec (cirrhose de Cruveilhier–Baumgarten). *Presse méd.* **44**:847-849, 1936.
11. Catti, G. Ueber Venengeräusche bei der interstitiellen Hepatitis. *Ztschr. f. klin. Med.* **61**:269-280, 1907.

MEDICAL PROGRESS

ECZEMA*

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A DIAGNOSIS of "eczema" is never a sufficient one. In recent years the term has come to be used more and more for those cases in which there is a suggestion that the cause of the dermatitis is allergy, and that the eczema depends on a sensitiveness to one or another foreign substance that affects the patient either by ingestion, by inhalation or by direct contact.

The present conception of eczema is remarkably new. In 1892, Besnier[1] wrote a "*Première nôte et observations prèliminaires pour servir d'introduction à l'étude des prurigos diathèsiques.*" He recognized that certain dermatoses that came and went in attacks depended on something wrong with the body as a whole and were not merely a disturbance that was limited to the skin itself. It was twenty-two years later, in 1914, that Rasch,[2] a Norwegian, named eczema of a certain variety "prurigo of Besnier." The description referred to the type of eczema which occurs in older children and young adults, and in which the distribution of lesions to the face, neck and antecubital and popliteal spaces is particularly characteristic. Brocq called it "*neurodermite,*" as Hill[3] has explained, but in more recent years it has passed under the name of "flexural eczema" and sometimes of "eczema with lichenification." Nowadays it is best designated as "atopic" dermatitis or perhaps "allergic dermatitis" or "atopic eczema," the adjective "atopic," proposed by Coca,[4] referring to the factor of inheritance, as well as to a mechanism comparable to that of hay fever and asthma.

Meantime, Schloss's[5] study of the baby sensitive to eggs, almonds and oatmeal was published in 1912. Goodale[6] described horse asthma in 1914, and in 1916 came the first comprehensive paper on human sensitization — that by Cooke and Vander Veer.[7] Also in 1916, Blackfan[8] tested eczematous infants with various substances and demonstrated that a high proportion of them were skin-sensitive to egg white. This paper furnished the first real evidence that allergy may be a factor in infantile eczema. The comprehensive studies of Walker[9] on asthma began in 1917. In 1920, Ramirez[10] likewise made skin tests on infants with eczema and showed that 30 of 78 cases were skin-test positive. At the same time he pointed out that those children who suffered also from asthma and hay fever were likelier than others to show positive skin reactions.

Treatment on the basis of eliminating certain foods, especially eggs and cow's milk, from the diet began. In 1923, O'Keefe[11] found that the diet treatment was successful even though he was unable to demonstrate positive skin tests, and he first pointed out that "variations in the threshold of sensitivity in various tissues may be the factor which determines whether hay fever, asthma or eczema will result from foreign proteins with which the tissues are brought in contact."

In the meantime, another type of eczema was in process of description when Bloch[12] found that

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when certain chemical substances like quinine, iodoform and turpentine were applied to the unbroken skin and were held in contact for some hours, areas of typical eczema developed on the test site. He came to the conclusion that the so-called "constitution of the skin" was the decisive factor in producing the reaction. Thus, when a patient with horse asthma was tested by this patch test with horse protein, an area of eczema developed in the arm, whereas when normal persons were tested in the same way, no reaction resulted. For some years it was not appreciated that the kind of eczema associated with asthma and hay fever and dependent on a factor of inheritance was quite different from the other kind of eczema that was localized to exposed surfaces and dependent on direct sensitization of a small area of exposed skin.

Recently, Cooke[13] has questioned the propriety of distinguishing so sharply between atopic eczema and contact dermatitis. Whereas it is quite true that both disorders depend on allergy, the facts, first that atopic eczema is often associated with other evidences of allergy whereas contact dermatitis is not, second that atopic eczema is not nearly so frequent as contact dermatitis, — the incidence of poison ivy, for example, is admittedly high, — and third that passive transfer antibodies (reagins) can be demonstrated in atopic eczema but not in contact dermatitis, make it reasonable to distinguish them.

Classifications

Many authors have classified eczema. Several old names based on the clinical appearance — the morphology of the eczema — have been given up, and new names have been added. Seborrhea, with its oily skin and distribution to the hair line, the face and the upper portions of the chest and back, probably does depend on a disturbance of the skin itself.

Fungus disease, often hard to distinguish from eczema, is found oftener on the feet and hands, in the crotch, in the axillas and sometimes on the neck. In most cases it is possible to recognize the two types of eczema due to allergy. In atopic dermatitis, the characteristic feature is the typical distribution of the lesions to the face, neck and cubital and popliteal spaces. Skin tests made by the scratch or intradermal method show immediate positive reactions of the wheal and erythema type, and reagins that can transfer the skin sensitiveness to a local test site on the arm of a normal person are found in the blood. In contact dermatitis, the lesions are on exposed parts — usually the hands and face. Here the foreign substance reaches the skin by direct contact and not through the blood stream underneath. Whether this type depends also on heredity is not clear; the majority of people are sensitive to poison ivy, and in industry the frequency of dermatitis that involves the hands and sometimes the face is greater than that of hay fever or asthma.

Atopic dermatitis can be divided for convenience into the infantile and adult types. In both, itching is the most significant feature. In infancy the lesions are on the face, where vesiculation and later oozing and crusting are characteristic. In older children and young adults vesiculation is not so marked, and in place of it comes lichenification, with thickening of the skin and later pigmentation. Although it is probably true that the two kinds of eczema differ chiefly in the location and concentration of sensitizing antibodies and so in the degree of clinical involvement, and that the differences may be greater in quantity than in kind, it is of practical importance to distinguish them, if only because in the one type the investigator looks for food or dust as the cause, whereas in the other he considers cosmetics, soaps and dyes, as well as chemicals in wide variety.

Atopic Eczema in Childhood

Hill[3] has written, "To talk about eczema is easy; to cure the patient is quite another matter." In 1935 he[14] wrote an extremely interesting paper on the evolution of atopic dermatitis. He showed how the infantile form may subside of itself within a year or two when the child outgrows his sensitiveness, whereas in other cases this early type merges by slow degrees into the adult type, with thickening in place of weeping. Hill believes that the presence of a positive skin reaction to egg, which is observed in at least half the cases, is easy to explain. Egg is a protein easily digested by the adult; it is a common food, and it has been shown that egg can pass unchanged through the intestinal wall and the placenta so as to sensitize the fetus in utero. The significance of the positive skin test is not quite so easy to explain. In some cases there is great improvement when egg is withdrawn from the diet, but in most it is impossible to demonstrate any clinical relation between the elimination of egg and the improvement of the eczema: indeed, most of the infants have never had egg. Moreover, as Hill explains, it is not possible to produce atopic sensitization in a normal nonatopic person no matter how much egg white may have been given by injection. "Precipitins," he writes, "are produced but never eczema, asthma or hay fever. . . . The infant is prepared for eczema by his sensitivity to egg, but the actual eczema may be brought about by other causes of which nothing definitely is known." Smyth et al.[15] were able to produce striking relief in 47 of 160 cases by changes in diet based on the finding of positive skin reactions to foods.

After 1935 there was a hiatus in the study of infantile eczema. Sulzberger and his co-workers[16–19] did much to clarify the relations between this and other forms of skin disease. In 1940, Hill[20] presented a useful discussion of the diagnosis and treatment,

including the importance of skin tests. In the next year he with Pratt[21] showed that in those infants sensitive to cow's milk the lactalbumin caused more trouble than the casein. It is to be wondered whether cottage cheese might not be a useful addition to an otherwise restricted diet.

In the meantime, Hampton and Cooke[22] and later Simon[23] discovered that human dander contains an allergen to which certain human beings become sensitive and that in certain infants the eczema depends on an allergy to human dander. Hampton and Cooke found that skin reactions to human dander were positive in a few cases but not in enough to support the idea that this dander is a frequent cause of eczema. Simon, on the other hand, found that skin tests by the patch method applied to young children with eczema showed positive reactions to human dander in 15 of 20 cases, whereas in 23 non-eczematous children of the same age there was only a single positive reaction. In a few cases, the prompt improvement that followed the avoidance of contact with human dander was striking. Finally, Simon was able to show that the lesions could be reproduced when, for example, the mother rubbed her hair on the lower abdomen of her child. In another paper he[24] found that extracts made from the scales of patients with seborrheic dermatitis gave reactions quite like those of human dander, whereas the scales from patients with psoriasis or exfoliative dermatitis showed nothing. All this work was done by the patch method of testing, since the scratch test remained negative.

One may conclude that in infantile eczema the factor of allergy is present, and in certain cases the lesions disappear when contact with the food or possibly with the dust is removed. On the whole, however, it is recognized more and more that in these children there is some fundamental disturbance that remains unexplained.

Several papers suggest the new trend. Engman and MacCardle[25] found that albino rats when fed a diet deficient in magnesium developed lesions similar to those of neurodermatitis. The vitamins have been studied, as might be expected. Kunz[26] examined the riboflavin metabolism in 2 cases. Harris and Gay[27] treated 20 cases of infantile eczema with large doses of vitamin B complex. In 2 of them there was complete healing and in 11 there were various degrees of improvement, but in 7 cases there was no change. The absorption of vitamin A was found by di Sant'Agnese and Larkin[28] to be impaired in 4 cases, but each patient was in extremely poor general condition, besides having severe eczema. On the other hand, Frei[29] varied the amount of vitamin A (carotene) in the diet of guinea pigs and studied the ability to sensitize them to old arsphenamine. No significant influence could be demonstrated.

More promising, perhaps, is a new suggestion about fat in eczema. Burr[30] showed pictures of a child before and after treatment with two or three teaspoonfuls of lard each day for a month. The eczema cleared entirely, and the author explains that fat has a sparing action on vitamin B_6, that linoleic acid is important to the health of the skin, and that rats fed on a fat-free diet develop scaly skin with retarded growth, and later kidney lesions. This paper is reminiscent of older theories that eczema depends on too much fat in the diet.

Atopic Dermatitis in Young Adults

In the Army and Navy, eczema is always troublesome, although fortunately the number of cases is not great. In 1943, French[31] reporting on allergy clinics in the Fourth Service Command, included 1100 cases of eczema as against 8500 cases of asthma and 5300 cases of hay fever. In the Navy, on the other hand, allergic skin diseases, according to Sulzberger,[32] comprised 8875 cases, whereas asthma and hay fever together numbered only 1257 cases. There were altogether 33,539 cases of skin diseases in the area described. Hampton and Rand[33] studied those men who were examined for certificates of disability for discharge on account of diseases of allergy. Of 1633 subjects, 286 had asthma, and 86 of them were discharged; 448 had hay fever, and 1 was discharged; 117 had urticaria, and 7 were discharged; 24 had atopic eczema, and 2 were discharged; and 35 had contact dermatitis, and 1 was discharged. Gold and Bazemore,[34] of Camp Blanding, give the clinic admission rate for asthma as 9.5 per 1000, for hay fever 3.3 and for eczema 12.3. The considerable variation of these figures is interesting; in some areas asthma seems much more important than eczema, whereas in other places the conditions are reversed. Presumably, the discrepancies depend on the difficulty of accurate diagnosis or on the classification used.

In the atopic dermatitis of adults, hypersensitiveness to foods plays a part in not over 10 or 15 per cent, according to Osborne, Jordon and Hallett.[35] In their paper, stress is laid on external contact and environmental allergy pointing to wool, silk, feathers, other epidermals, soaps and laundry chemicals. As they say, a visit to the home of the patient is indispensable. Stroud[36] has commented on this, writing, "Success in the treatment of allergic dermatitis is proportionate to knowledge of the causative factors." Hill[37] has shown that with increasing age the importance of environmental allergy (dust substances) rapidly increases. Scratch tests with dusts were positive in only 10 per cent of 38 eczematous infants, but after the age of one they became positive in 37 per cent and after two in 50 per cent. Feinberg[38] stresses the molds, describing 14 cases in which the eczema became much worse during the pollen and mold seasons. In a number of patients, I have found that the eczema cleared when the patient went away from home and recurred on his return. Such a history is always im-

portant and emphasizes once more the need for great care in history taking. It is always worth while to repeat the two most important points. First, one should record the passage of time and the relation to various foods and events by the actual dates on which they occurred and try to explain the end of the attack just as carefully as the onset. Secondly, one should account for all the time from the beginning of the disease to the present. If there was an interval of a year or two or perhaps of only a few months in the summer when the skin was quite clear, it is essential that this fact be noted in the history. Often such knowledge leads to the discovery that during the free period the patient was sleeping in a different house or perhaps living and sleeping in a different room in his own home.

Some years ago, Becker[39] laid stress on the fact that treatment of the patient as a whole was quite as important as treatment of his eczema. A woman who had had an eruption on the neck was playing thirty-six holes of golf every day and was in a state of chronic fatigue. With proper advice directed toward the improvement of general hygiene, the eczema cleared, even though contact with necklaces, dresses and a mink coat were the same after as before her visit to the physician.

The treatment of atopic eczema in adults is not easy; there is no specific treatment. Local treatment is necessary, but one should realize that the ointment or wash that does good in one case may be useless in the next. All too often one finds that too much local treatment does more harm than good. Potassium chloride, extra vitamins and nonspecific therapy of various kinds have all been used with success in certain cases but without effect in others. The ingestion of lard mentioned above for infantile eczema has been tried in older patients by Finnerud, Kesler and Wiese[40] with little evidence of success.

Contact Dermatitis

In writing a review of the literature of drug allergy, I[41] was impressed by finding that in different patients the same drug might cause a variety of manifestations. Arsenic, for example, might cause in different cases a diffuse generalized dermatitis medicamentosa, asthma, agranulocytosis or a local contact dermatitis. This finding was an excellent demonstration that sensitiveness depends on the concentration of antibodies in certain tissues that are more sensitized than others. As described above, the principles of contact dermatitis are somewhat the same as those for atopic eczema, but they vary in degree; the sensitiveness is not general but is often confined to one area of the skin. The so-called "fixed drug eruptions" are particularly interesting, for in this condition the patient has a certain spot, perhaps on the thigh, face or arm, that always flares up when the drug is taken by mouth or by hypodermic needle. This is hardly a contact dermatitis, but it illustrates the principle of localized tissue sensitiveness.

Contact dermatitis becomes increasingly important in industry as more and more complex chemical substances are devised. In contact dermatitis, the typical lesions are often on the hands; the backs of the fingers flare when the surgeon puts on the wrong kind of rubber gloves or the pharmacist or dentist comes in contact with novocain or quinine or other chemicals. They may be on the face, much trouble arising from cosmetics. Hazen[42] declares that the most frequent cause of dermatitis of the eyelids is nail polish. Howell[43] found that all brands of nail polish could cause the trouble, and Shelton[44] incriminated the nail-enamel foundation. Epstein[45] described the case of a mother and two daughters, aged four and six, who developed a contact dermatitis from hair lacquer pads. In the children the lesions at first suggested mumps because of the distribution and swelling, but later on, patch tests with the lacquer pads gave positive reactions. Pyle and Rattner[46] report the case of a medical officer who developed an inflammation of the eyelids and conjunctivas while preparing solutions of penicillin. Schwartz[47] has described 1904 cases constituting 30 per cent of those who worked in an explosive factory producing tetryl. The face, neck, eyes and all parts touched with the soiled hands are involved, and if exposure continues anemia and leukopenia may follow. Schwartz, Peck and Dunn[48] describe a dermatitis that depends on ureaformaldehyde and phenolformaldehyde resins, and Peck[49] finds that certain cutting oils and solvents that remove the fats and oils and dry the skin cause a local dermatitis. Baker's eczema is not frequent. At first it was thought that the trouble came from the ammonium persulfate and other substances added to the flour to make it easier to handle, but patch tests with these substances showed no reactions, and Van Vonno and Struycken[50] concluded that the trouble depended on the wheat flour itself.

The reactions that come from the sulfonamide drugs are of more practical interest. These are of great variety, ranging from a severe generalized exfoliative dermatitis in the case described by Johnson[51] to a local reaction when a drug is applied for local treatment. Kasselberg[52] described the case of a young man who had been treated with sulfathiazole for gonorrhea. Twenty days later the drug was changed to sulfamerazine, and after forty-eight hours a generalized macular eruption appeared, which three days later turned into a pemphigus-like disease, with numerous bullas and blebs filled with straw-colored fluid. One forgets that to produce sensitiveness, either local or general, one must follow the principles of the classic anaphylaxis experiment with its three factors — first the sensitizing dose, second a time interval and third the test or shocking dose. Park[53] has described 12 cases in which local sulfonamide therapy resulted in a cu-

taneous hypersensitiveness to the drug, and he cautions against the indiscriminate use of sulfonamides in local treatment, which may sensitize the patient and so preclude the subsequent use of these drugs should serious illness supervene. Shaffer, Lentz and McGuire[54] have also found that sensitiveness to sulfathiazole can be induced by local therapy and subsequently elicited by oral medication.

As a test for sulfonamide hypersensitiveness, Leftwich[55] has made an important contribution. In tests for drug allergy, the application of most drugs by themselves to the skin produces no local reaction. The reaction must depend on a chemical combination between the drug and the serum protein. Leftwich found that the serum of patients who are saturated with the sulfonamide drugs and whose blood level is therefore high is an extremely useful testing agent. It is important that the donor patient shall have received the drug for at least five days and that the serum be used fairly soon after its separation. It is also important that the serum from a normal person be drawn at the same time and be kept under the same conditions so that the observations can be controlled. Leftwich reports that when the sulfonamide-bearing serum was injected intradermally into 30 patients who were clinically sensitive to the sulfonamide drugs, the results were positive in 28, with a wheal and erythema reaction that appeared in fifteen minutes. This may be significant particularly if the findings can be confirmed.

The legal aspects of contact dermatitis, especially in connection with industry and occupation, are sometimes complex. The employer has provided the specific substance, but the worker has provided the kind of tissue that is capable of developing a sensitiveness to that substance. Each of the two factors is necessary, and it is not always easy to separate them. Downing[56] has discussed the matter in an interesting paper.

* * *

To repeat, the diagnosis of eczema is never a sufficient one. The problem is always complicated, but if one tries to visualize the probable mechanism that is operating in the particular patient, it is easier to find the cause through a better classification of the possible factors. As usual in the study and treatment of all the diseases due to allergy, it is the clinical history taken from the point of view of the detective more than from that of the physician that leads to the proper solution. In doing this, however, one must at least know what the possibilities are. In the background of all these cases there is a fundamental disturbance of normal physiology; this is a platitude that cannot be disregarded.

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References

1. Besnier, E. Première note et observations préliminaires pour servir d'introduction à l'étude des prurigos diathésiques (dermatites multiformes prurigineuses chroniques exacerbantes et paroxystiques, du type du prurigo de Hebra). *Ann. de dermat. et syph.* **3**:634-648, 1892.
2. Rasch, C. Cited by Barber, H. W., and Oriel, G. H. Clinical and biochemical study of allergy. *Lancet* **2**:1009-1013, 1928.
3. Hill, L. W. Chronic atopic eczema (neurodermatitis) in childhood. *J. A. M. A.* **103**:1430-1434, 1934.
4. Coca, A. F., and Cooke, R. A. Classification of phenomena of hypersensitiveness. *J. Immunol.* **8**:163-182, 1923.
5. Schloss, O. M. Case of allergy to common foods. *Am. J. Dis. Child.* **3**:341-362, 1912.
6. Goodale, J. L. Anaphylactic reactions occurring in horse asthma after administration of diphtheria antitoxin. *Boston M. & S. J.* **170**:837, 1914.
7. Cooke, R. A., and Vander Veer, A., Jr. Human sensitization. *J. Immunol.* **1**:201-305, 1916.
8. Blackfan, K. D. Cutaneous resection from proteins in eczema. *Am. J. Dis. Child.* **11**:441-454, 1916.
9. Walker, I. C., and Adkinson, I. Studies on staphylococcus pyogenes aureus, albus and citreus, and on Micrococcus tetragenus and M. catarrhalis. *J. Med. Research* **30**:373-390, 1917.
10. Ramirez, M. A. Protein sensitization in eczema. *Arch. Dermat. & Syph.* **2**:365-367, 1920.
11. O'Keefe, E. S. Protein sensitivity in children with negative cutaneous reactions. *J. A. M. A.* **80**:1120, 1923.
12. Bloch, B. Eczema and diathesis. *Ztschr. f. klin. Med.* **99**:2-14, 1924.
13. Cooke, R. A. Consideration of some allergy problems. I. Allergic dermatitis (eczema). *J. Allergy* **15**:203-211, 1944.
14. Hill, L. W., and Sulzberger, M. B. Evolution of atopic dermatitis. *Arch. Dermat. & Syph.* **32**:451-463, 1935.
15. Smyth, F. S., Bain, K., and Stallings, M. Infantile eczema: study based on one hundred and sixty cases. *J. A. M. A.* **97**:1291-1295, 1931.
16. Sulzberger, M. B. Some recent advances in diagnosis and treatment of diseases of skin. *J. Connecticut M. Soc.* **1**:83-91, 1936.
17. Sulzberger, M. B., and Goodman, J. Nomenclature, definition, and classification of allergy and allergic manifestations. *M. Rec.* **143**: 17-19, 1936.
18. Sulzberger, M. B., Wise, F., and Wolf, J. Tentative classification of allergic dermatoses. *J. A. M. A.* **104**:1489, 1935.
19. Sulzberger, M. B. *Dermatologic Allergy.* 540 pp. Springfield, Illinois: Charles C Thomas, 1940.
20. Hill, L. W. Eczema in infants and young children. *New Eng. J. Med.* **223**:624-626, 1940.
21. Hill, L. W., and Pratt, H. N. Sensitivity to casein in infantile eczema confirmed by biologic titratrin of testing extract. *J. Allergy* **12**: 143-153, 1941.
22. Hampton, S. F., and Cooke, R. A. Sensitivity of man to human dander, with particular reference to eczema (allergic dermatitis). *J. Allergy* **13**:63-76, 1941.
23. Simon, F. A. Human dander: important cause of infantile eczema. *J. A. M. A.* **125**:350, 1944.
24. *Idem.* On allergen in human dander. *J. Allergy* **15**:338-345, 1944.
25. Engman, M. F., Jr., and MacCardle, R. C. New approach to problem of disseminated neurodermatitis. *Arch. Dermat. & Syph.* **46**:337-347, 1942.
26. Kunz, A. F. Der Lactoflavinstoffwechsel in zwei Fällen von generalisiertem Ekzem bei vorwiegender Behandlung mit Rohkost. *Schweiz. med. Wchnschr.* **72**:1154-1158, 1942.
27. Harris, A., and Gay, L. N. Use of vitamin B complex in treatment of infantile eczema. *J. Allergy* **14**:182-184, 1943.
28. di Sant'Agnese, P. A., and Larkin, V. deP. Vitamin A absorption in infantile eczema. *Proc. Soc. Exper. Biol. & Med.* **52**:343, 1943.
29. Frei, W. Further studies in arsphenamine hypersensitiveness in guinea pigs. IV. Vitamin A (carotene) in relation to sensitization of guinea pigs to old arsphenamine. *J. Invest. Dermat.* **5**:117-126, 1942.
30. Burr, G. D. Significance of essential fatty acids. *Federation Proceedings* **1**:224, 1942.
31. French, S. W. Report on allergy clinics in Fourth Service Command, November 1, 1942 to November 1, 1943. Official Publication, U. S. Army, November 1, 1943.
32. Sulzberger, M. B. Allergic skin diseases in Navy. *Ann. Allergy* **2**: 5, 1944.
33. Hampton, S. F., and Rand, H. Problem of allergy at Army Air Forces Hospital. I. Respiratory allergy (hay fever, vasomotor rhinitis, and bronchial asthma). *J. Allergy* **15**:355-368, 1944.
34. Gold, E. M., and Bazemore, J. M. Significance of allergy in military medicine: report of incidence of allergic diseases in large station hospital, and method of preinduction evaluation of allergic state. *J. Allergy* **15**:279-282, 1944.
35. Osborne, E. D., Jordon, J. W., and Hallett, J. J. Practical management of eczema in infants and children. *New York State J. Med.* **42**: 47-50, 1942.
36. Stroud, C. M. Allergic dermatitis. *J. Allergy* **2**:118-124, 1931.
37. Hill, L. W. Sensitivity to environmental allergens in infantile eczema. *New Eng. J. Med.* **213**:135-140, 1935.
38. Feinberg, S. M. Seasonal atopic dermatitis: role of inhalant atopens. *Arch. Dermat. & Syph.* **40**:200-207, 1939.
39. Becker, S. W. Eczema: fundamental practical considerations. *J. A. M. A.* **97**:983-987, 1931.

40. Finnerud, C. W., Kesler, R. L., and Wiese, H. F. Ingestion of lard in treatment of eczema and allied dermatoses: clinical and biochemical study. *Arch. Dermat. & Syph.* **44**:849-861, 1941.
41. Rackemann, F. M. Allergy: with special reference to drug allergy. *New Eng. J. Med.* **224**:688-693, 1941.
42. Hazen, H. H. Dermatitis of eyelids. *Arch. Dermat. & Syph.* **49**:253, 1944.
43. Howell, J. B. Contact dermatitis from hair lacquer. *J. A. M. A.* **123**:408, 1943.
44. Shelton, J. M. Dermatitis due to nail polish foundation. *Arch. Dermat. & Syph.* **48**:197, 1943.
45. Epstein, S. Contact dermatitis caused by hair lacquer pads: characteristic clinical picture. *J. A. M. A.* **123**:409, 1943.
46. Pyle, H. D., and Rattner, H. Contact dermatitis from penicillin. *J. A. M. A.* **125**:903, 1944.
47. Schwartz, L. Dermatitis from explosives. *J. A. M. A.* **125**:186-190, 1944.
48. Schwartz, L., Peck, S. M., and Dunn, J. E. Dermatitis from resin glue in war industries. *Pub. Health Rep.* **58**:899-904, 1943.
49. Peck, S. M. Dermatitis from cutting oils, solvents and dielectrics, including chloracne. *J. A. M. A.* **125**:190-196, 1944.
50. Van Vonno, N., and Struycken, J. Untersuchungen über die Entstehung des Backerekzems. *Dermat. Ztschr.* **67**:43-82, 1933.
51. Johnson, R. D. Generalized exfoliative dermatitis due to sulfadiazine. *J. A. M. A.* **124**:979, 1944.
52. Kasselberg, L. A. Severe pemphigus-like reaction following administration of sulfamerazine. *J. A. M. A.* **123**:1035, 1943.
53. Park, R. G. Cutaneous hypersensitivity to sulphonamides: report of twelve cases. *Brit. M. J.* **2**:69-72, 1943.
54. Shaffer, B., Lentz, J. W., and McGuire, J. A. Sulfathiazole eruptions: sensitivity induced by local therapy and elicited by oral medication: report of four cases with some allergic studies. *J. A. M. A.* **123**: 17-23, 1943.
55. Leftwich, W. B. Intradermal test for recognition of hypersensitivity to sulfonamide drugs. *Bull. Johns Hopkins Hosp.* **74**:26-48, 1944.
56. Downing, J. G. Dermatophytosis and occupational dermatitis. *J. A. M. A.* **125**:196-200, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31221

PRESENTATION OF CASE

A fifty-five-year-old Polish woman was admitted to the hospital complaining of anorexia, weakness and intractable vomiting.

For the past ten years she had had vague epigastric discomfort, with a feeling of tightness across the abdomen. During this same period she took laxatives frequently for constipation. There had been insidious weight loss for probably a long period. During the past five years the epigastric discomfort had become distressing, with occasional nausea and vomiting. For the past four years there had been infrequent episodes of bright-red bleeding from the rectum. About one and a half months before admission she began to vomit frequently. The vomiting was preceded by epigastric distress varying from a feeling of fullness to moderately severe pain. Vomiting always brought relief. Malaise was pronounced during the month before entry. For about three weeks she had coughed up small amounts of bright blood on occasions.

She had had pneumonia one year before admission, from which she recovered uneventfully. She was seven years postmenopausal.

Physical examination revealed a pale, thin, slightly icteric woman with evidence of a moderate amount of recent weight loss. Many teeth were absent, and the remainder carious. The heart size and rhythm were normal. A mild systolic murmur was heard at the apex. The lungs were clear and resonant. The abdomen was flat. There was a moderately enlarged, tender liver, extending five fingerbreadths below the costal margin. On inspiration a questionable, firm, tender mass was felt in the epigastrium. The tip of the spleen was just palpable beneath the costal margin on inspiration. Pelvic and rectal examinations were negative.

The temperature was 101°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 65 diastolic.

Examination of the blood showed a white-cell count of 11,000, with 64 per cent neutrophils, 28 per cent lymphocytes, 6 per cent monocytes and 2 to 3 per cent of what were thought to be metamyelocytes. Examination of the urine showed a specific gravity of 1.030; it contained no albumin, and a test for sugar was green to orange with Benedict's solution. The sediment showed an occasional red and white cell. The stool was guaiac negative. A Hinton tset was negative. The serum protein was 7.95 gm. per 100 cc., with an albumin-globulin ratio of 0.5. The chloride, nonprotein nitrogen and van den Bergh test were normal. The phosphorus was 2.7 mg. per 100 cc., and the alkaline phosphatase 2.1 Bodansky units. The prothrombin time was 35 seconds (normal, 18 to 20 seconds).

X-ray examination of the chest and a gastrointestinal series were normal. An intravenous pyelogram showed a large liver extending to the level of the iliac crest. The right kidney was unusually low in position but was normal in shape and function; the left kidney was normal. A barium enema showed the hepatic flexure to lie extremely low in the abdomen. Proctoscopic examination showed intrinsic disease of the rectum and lower sigmoid.

On the first day the patient passed a small blood clot with her bowel movement, but no bright blood; the stool was of normal color. Occasionally she vomited bile-stained material. Further serum studies a week after admission showed a total protein value of 7.16 gm. per 100 cc., with an albumin-globulin ratio of 0.28. The cholesterol value was 53 mg. per 100 cc., with esters too low to read. The van den Bergh reaction was 17.6 mg. per 100 cc. direct and 28.4 mg. indirect. The cephalin flocculation test was ++++, and the prothrombin time 49 seconds (normal, 18 to 20 seconds); later the prothrombin time increased to 54 seconds. The white-cell count

*On leave of absence.

became gradually elevated to 20,000, with 75 per cent neutrophils, 9 per cent lymphocytes and 16 per cent monocytes; toxic granules were prominent. Despite repeated transfusions the red-cell count could not be maintained above 3,000,000. The urine showed increasing amounts of bile, with a ++ to +++ test for albumin and considerable sugar during intravenous glucose therapy. The patient had frequent chills, with occasional fever, while receiving amino acids (Amigen) intravenously. The size of the liver remained unchanged, but it became more tender.

During the third week the patient developed a mousy odor to her breath and the jaundice deepened, with the appearance of dullness and rales at both bases, ascites and sacral edema. She became depressed, stuporous and finally semicomatose, with an erratic temperature and pulse. She had three days of subnormal temperature and expired quietly on the twenty-third day.

Differential Diagnosis

Dr. Joseph C. Aub: Here is a woman who had epigastric fullness and discomfort, which suggest increased portal pressure because of the association with occasional gastrointestinal bleeding. The record implies that there was nothing wrong above the diaphragm and that all the difficulty lay in the abdomen. We are dealing with a large liver, possibly an enlarged spleen and an epigastric mass.

I should like to see the x-ray films, with particular reference to the epigastric mass that is mentioned, as well as the condition of the bones. My interest in the bones is based on the extraordinary albumin-globulin ratio, which discloses such a high level of globulin that one must consider the presence of multiple myeloma.

Dr. Milford D. Schulz: These films show the liver edge extending below the crest of the ilium. The right kidney apparently has rotated and overlies the crest of the ilium.

Dr. Aub: You see no evidence of the epigastric mass?

Dr. Schulz: No. The spleen does not seem large; you can see its tip about where that of the normal spleen usually appears.

I do not believe that the chest is normal. There is something in the right apex. I cannot be sure whether it is in the lung or in the pleura. It is what has been called thickened apical pleura, but may represent atelectasis in the upper lobe. The bones, so far as one can see, are quite all right.

Dr. Aub: The patient had an erratic temperature, which suggests sepsis. One or two times it went up to 104°F., apparently owing to the injection of amino acids.

Here then is a woman with a fever, who had had symptoms for five years, and who entered the hospital with a big liver and no intense amount of liver damage. The liver deteriorated rapidly, according to the history, and she died with evidence of severe liver damage. I think that one can rule out obstructive jaundice or difficulty with the bile ducts on that basis. I believe that this woman had severe damage to the hepatic cells themselves, and that she died of cholemia.

The albumin-globulin ratio in the blood interested me, for there was a high total protein, made up mostly of globulin, the albumin being extremely low. One must discuss four diagnoses: myeloma, amyloidosis, hemochromatosis and cirrhosis.

This woman had severe liver damage, but the blood changes were so marked that one wonders whether they could have been due to liver damage. The alternative is to think of myelomatous lesions in the bones. Bone lesions are not essential, however, since this tumor may be found only in the liver. Later in the disease she had a great deal of albuminuria but no Bence–Jones protein in the urine. There is also the queer finding of a couple of metamyelocytes in the blood, which might have been a misdiagnosis of the plasma cells found in multiple myeloma. I should like to make a diagnosis of multiple myeloma but it is unwise to do so, because it is a rare disease and because there is not enough evidence for it in this record.

The next thing that occurred to me was amyloid disease. Albumin in the urine, without abnormality of the sediment, always suggests amyloid disease to me. Was a Congo red test done?

Dr. Benjamin Castleman: No.

Dr. Aub: The spleen was not particularly large, but I have seen many cases of amyloid disease in which there was no justification for making the diagnosis. It is an interesting point, but without the Congo red test I am incapable of making the diagnosis.

This record does not contain evidence of jaundice sufficiently severe to justify the diagnosis of acute yellow atrophy of the liver. In other words, the diagnosis that must be made involves a big liver that was not functioning. It could have been a fatty liver, early in cirrhosis, but I do not believe that that is likely. She had several other noteworthy findings, namely, an extremely low cholesterol and no cholesterol esters in the blood, which imply severe liver damage, and a normal phosphatase, indicating, however, that the liver cells were not being rapidly destroyed. Amyloid disease should be entertained as a serious possibility.

In favor of hemochromatosis is the sugar in the urine even though the blood-sugar level is not given.

Dr. Chester M. Jones: But that was following intravenous glucose therapy.

Dr. Aub: The urine is reported to have given a green reaction with Benedict's solution on entrance to the hospital, but this is not adequate evidence for hemochromatosis.

The fourth thing is cirrhosis. I think that she had a mild cirrhosis, not enough to give ascites and therefore not a severe cirrhosis. With an albumin-

globulin ratio such as she exhibited there must have been little cirrhosis. Severe cirrhosis should give quite marked ascites, because most of the osmotic pressure in the blood is produced by albumin rather than by globulin. With the evidence in the history suggesting a high portal pressure I think one should make a diagnosis of a mild degree of some form of cirrhosis.

One ends up with the question whether she had a tumor. On the basis of mild cirrhosis she could have had multiple liver-cell carcinomas or hepatomas, accompanied by so-called "carcinomatous cirrhosis." That is a perfectly good diagnosis and would explain the fever, because most patients with carcinoma of the liver have a fever, usually from necrosis in the center of the tumor. Such tumors may be myelomatous.

I can make one definite diagnosis, saying that this patient died of severe liver damage, cholemia, in spite of a large liver. I believe that she had a mild degree of cirrhosis. The other diagnosis lies between those that I have mentioned and cannot, I think, be stated with conviction, but I favor a diagnosis of multiple hepatomas.

DR. PAUL C. ZAMECNIK: Our impression was that the patient had Laennec's cirrhosis to begin with, even though there was no evidence of alcohol ingestion. We also thought that she had a superimposed toxic hepatitis or subacute yellow atrophy.

DR. AUB: I did not discuss that possibility because I thought that the slight degree of jaundice on entrance was much against that diagnosis.

DR. ZAMECNIK: It is interesting that during hospitalization she was able to take little by mouth and was largely fed intravenously. As our efforts failed, we decided to try amino acids. Certain members of the staff suggested that in the face of a failing liver amino acids might be an additional burden. Our experience in giving amino acids for a day or two was that the patient's temperature rose and the jaundice deepened, so that we discontinued this therapy, believing that it did her no good.

DR. JONES: I should like to comment on one remark that Dr. Aub made relative to amyloid disease. I do not believe that I have ever seen a case of amyloid disease with hepatic failure and this degree of jaundice. If it occurs, I am not familiar with it. It would not have occurred to me as a possibility. I should think that one would have to include metastatic disease, and I wonder whether metastatic lesions of a cancer of the pancreas ought to be considered.

CLINICAL DIAGNOSIS

Portal cirrhosis, with superimposed toxic hepatitis.

DR. AUB'S DIAGNOSES

Cholemia, due to liver cell destruction.
Cirrhosis of liver, mild.
Multiple liver-cell carcinoma.

ANATOMICAL DIAGNOSES

Acute hepatitis.
Portal cirrhosis?
Bile nephrosis.
Ascites.
Splenomegaly.
Pulmonary tuberculosis, old.
Tuberculous ulcer of ileum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The liver weighed slightly under 1500 gm. and was extremely tough. One could not put one's finger through the parenchyma, even with the fingernail, indicating the presence of a large amount of connective tissue. It was yellow to greenish brown, with scattered areas of fibrosis. Although the liver was fibrotic, there was no granularity of the surface. One could not make out individual nodules of regeneration on the surface, such as are found in portal cirrhosis. There were also a large number of yellow-orange areas that we believed were foci of necrosis.

Microscopical examination showed few remaining normal liver cells. Most cells were large, swollen and necrotic. Many near the areas of degeneration had four or five nuclei in them, a finding indicating active regeneration or hyperplasia of the liver cells. These multinucleated cells were observed in many of the cases of epidemic jaundice recently reported by Lucké.* In many of the portal areas that could be identified there were lymphocytic and polymorphonuclear infiltration and definite fibrosis. There was in this case, therefore, a severe, acute hepatitis that might be likened to that in cases of epidemic jaundice and that may have been due to a virus or a toxin of some sort. This patient's illness was of ten weeks' duration and I do not believe that so much fibrosis could have been produced in that time. I suppose one has to assume, as Dr. Aub did, that there was an underlying disease that had existed for years, probably a mild cirrhosis. I have recently shown these slides to Lieutenant Colonel Tracy B. Mallory, who believes that this amount of fibrosis can be produced in as short a period as ten weeks. If that is so, we do not have to assume an underlying cirrhosis. The toughness of the gross specimen, however, is in keeping with an old process, which lessened the chances of recovery.

The kidneys were large, weighing 700 gm., and showed a bile nephrosis. The peritoneal cavity contained 1500 cc. of yellowish fluid. The spleen was about twice the normal size, weighing 350 gm.

The lesion in the right apex of the lung proved to be old tuberculosis. The cause for the blood in the stools was a tuberculous ulcer, 1 cm. in diameter, in the terminal ileum.

DR. JONES: More than once there has been objection to the term "hepatic failure" as the im-

*Lucké, B. Pathology of fatal epidemic hepatitis. *Am. J. Path.* 20: 471-593, 1944.

mediate cause of death, the certificates having been returned. It seems to me that we see a great many persons in whom, without an autopsy, it is impossible to make a diagnosis of the exact type of underlying liver disease and yet the cause of death is undoubtedly hepatic failure. There is an occasional tendency to say that this should be called acute yellow atrophy. In some cases there is a lot of destruction of liver cells, and in others, diffuse carcinomatosis or a similar infiltrative process. One can get this picture with cholemia and yet have no appreciable amount of necrosis. I think that hepatic failure is a good descriptive term for such a final event, just as uremia is in a patient with renal disease.

CASE 31222

Presentation of Case

First admission. A fifty-five-year-old business man was admitted to the hospital because of jaundice.

He appeared to be in excellent health until three weeks before admission, when he noticed that his urine had become dark, and his stools pale slate colored. The following week he developed anorexia and had frequent soft stools. The urine remained dark and the stools clay-colored until admission. Twelve days before entry it was first observed that he was jaundiced. He felt fairly well and on the following day played tennis; a day later he developed slight nausea. No pain, malaise, chills or fever was noted at any time. He was examined by his physician ten days before he was admitted. At that time the temperature, pulse and respirations were normal. There was marked icterus of the skin and scleras. He had lost no weight recently. The abdomen was negative. The liver and spleen could not be felt. An x-ray examination revealed no gallstones. The stool was negative for bile, and a cephalin-flocculation test was negative. The icteric index was 42 units. He was placed on a high-carbohydrate, low-fat diet supplemented with vitamins. The patient insisted on continuing his work at the office, where he worked until noon each day. During the week before admission he had three soft clay-colored stools a day and lost approximately 10 pounds in weight.

Six years before admission he had an "ulcer," which recurred a year before admission; both times he responded well to medical therapy. His bowel habits had been normal.

Physical examination revealed a well developed, fairly thin man who was deeply jaundiced but not bronzed. There was no lymphadenopathy. The lungs were clear, with good expansion. The right half of the diaphragm was quite high. The heart was normal in size, rate, rhythm and sounds. The liver edge could be felt three to four fingerbreadths below the costal margin; it was smooth, rounded and nontender. The spleen was not felt. There was no ascites or edema. Rectal and neurologic examinations were negative.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

The urine was dark, with a specific gravity of 1.026, gave a ++++ test for bile, and showed traces of albumin and sugar, with an occasional white cell, red cell and cast in the sediment; the test for urobilinogen was plus in dilution of 1:8. Examination of the blood showed 4,400,000 red cells, with 90 per cent hemoglobin (Sahli), and 8500 white cells. The stool was clay-colored and guaiac negative and contained no bile. The van den Bergh reaction was 11.8 mg. per 100 cc. direct, and 16.7 mg. indirect. The serum nonprotein nitrogen and protein and the prothrombin time were normal. The phosphorus was 3.0 mg. per 100 cc. The alkaline phosphatase was 10.2 units per 100 cc., and a cephalin-flocculation test was negative in forty-five hours.

X-ray examination of the gastrointestinal tract revealed the esophagus to be normal. The stomach contained a moderate amount of secretion and showed slight thickening of the mucosal folds. The duodenal cap was slightly deformed, without definite evidence of a crater. The remainder of the duodenal loop showed no evidence of a pressure defect. The liver appeared slightly enlarged, and the spleen normal. At six hours the barium was in the proximal colon. There were a few calcified nodes in the midportion of the abdomen.

The patient had a poor appetite, but with supplementary intravenous feedings he was maintained on a high-carbohydrate, high-protein, high-vitamin and low-fat diet. He was given an ampule of Hykinone each week. After three weeks his stool became somewhat darker and contained a small amount of bile. The van den Bergh reaction dropped to 9.0 mg. per 100 cc. direct, and 12.4 mg. indirect. The alkaline phosphatase fell to 6.4 units, and the test for urobilinogen in the urine was positive in dilutions up to 1:100.

After four weeks in the hospital the patient was discharged to his home under close observation and with a carefully selected diet. The temperature, pulse and respirations had remained normal, but he had lost 5 pounds and his icterus had not noticeably diminished.

Second admission (nineteen days later). In the interim he had become stronger; he walked about a mile each day but had lost 3 more pounds. His chief complaint during this time was heartburn, which usually came on several hours after meals. There was no nausea, and he was never wakened from sleep. Three days before admission he vomited for the first time, shortly after drinking a glassful of water. The vomitus contained only the fluid that he had recently drunk. On the following evening he again vomited. He spoke of vague, nonradiating discomfort in the epigastrium.

Physical examination showed no significant change. His icterus, nutritional status and sense of well-being were essentially the same. The liver was five fingerbreadths below the costal margin, and the spleen was not felt.

The urine gave a + test for albumin and a ++++ test for bile; the sediment contained an occasional white cell. The hemoglobin (photoelectric method), which had been 14.3 gm. at the time of discharge, was 12.8 gm. The white-cell count and differential were normal. The stool was clay-colored and guaiac negative and contained no bile. The prothrombin time was normal, but a cephalin-flocculation test was ++++ in twenty-four hours. The alkaline phosphatase was 7.8 units per 100 cc., and the van den Bergh reaction 9.28 mg. direct and 13.2 mg. indirect. The urobilinogen in the urine was positive in a dilution of 1:40.

A week after admission the alkaline phosphatase was 9.6 units per 100 cc. and the cephalin flocculation was negative. His diet was supplemented by intravenous feedings, and he received three transfusions. During one transfusion he had a chill and the temperature spiked to 101°F., otherwise the temperature, pulse and respiration remained normal. A laparotomy was performed on the twelfth hospital day.

Differential Diagnosis

Dr. Francis D. Moore: This case seems to me to contain elements suggesting various pathologic lesions. If one reads through most of the case one would say that the jaundice was painless, but then this must be qualified because later the patient did have some discomfort, characterized as epigastric pain. The jaundice was fluctuating. So it was fluctuating, obstructive, "almost painless" jaundice.

May we see the x-ray films? The main thing that I should like to find out from Dr. Schulz is whether this man did have an ulcer, or whether it was gall-bladder disease that the patient or his physician thought was an ulcer.

Dr. Milford D. Schulz: I think that he probably had an ulcer. The duodenal bulb is flat and slightly irregular. I do not believe there is anything shown by the films beyond what has been stated in the protocol.

Dr. Moore: He has no opaque gall stones, a little duodenal deformity but nothing striking and no widening of the duodenal loop, which is important.

Was the jaundice primarily obstructive, not being due to intrahepatic disease or excessive hemolysis? I think that it probably was. The direct to indirect ratio of the van den Bergh reaction was about 75 per cent, which favors such a diagnosis; this interpretation is not infallible, but in this hospital over a period of time it has been fairly reliable. The highest direct to indirect ratio was the first one obtained. Later, the patient apparently developed liver damage, as evidenced by the positive cephalin-flocculation test and also by a change in the ratio of the direct to indirect bilirubin in the direction characteristic of parenchymatous liver disease. The alkaline phosphatase was elevated on several occasions, which is in favor of obstructive jaundice. There was little urobilinogen in the urine when the patient was first admitted. Later it was high, and during the second admission it was about halfway between. To get urobilinogen in the urine there must be urobilinogen in the feces. This patient had urobilinogen in the urine at a time when he had a bile-free stool. That finding is inconsistent, but the amounts present do not support the idea that it was a hemolytic process, nor do the red-cell counts recorded in the protocol.

Can we dismiss an acute hepatitis? I think we can. The patient did not have fever. His liver enlarged slowly. When first seen, the liver was not large or tender, which I think is unusual for acute hepatitis, and he had clay-colored stools right from the start, even antedating the jaundice. He had a negative cephalin-flocculation test on the first admission, suggesting that early in the disease the liver cells were not working under too great a burden. Just before operation, the cephalin-flocculation test changed from positive to negative in a short time. I do not know enough about the test to be sure that that is suggestive of a change in status. I should rather believe that it was a laboratory phenomenon.

Then there are portal cirrhosis of the liver and one of its precursors to be considered. Against these are the facts that he had not developed ascites, that the serum was normal and that he had no esophageal varices.

So, narrowing ourselves down to obstructive phenomena of one sort or another, we have tumor on the one hand and stones on the other. Tumor usually produces a story of increasing jaundice that does not fluctuate. This man had definite fluctuation of bile in the stools and of his jaundice, suggesting that the obstruction let up for a while. That is in favor of a stone. In favor of tumor, however, is the relatively rapid onset in a man of fifty-five, with apparently little previous history of disease of any sort unless the ulcer story was really gall-bladder disease.

One other fact that I think is important is that he did not have a palpable gall bladder. If the obstructive jaundice had been due to neoplasm involving the biliary tree from the junction of the cystic and common ducts downward we should expect him to have developed a big, soft, nontender, palpable gall bladder. The fact that he did not have that in the presence of jaundice, which was apparently obstructive, suggests that it was due to stone and that the reason the gall bladder did not enlarge was that it was involved in old chronic cholecystitis. One might argue the other way, and say that he had carcinoma of the gall bladder, which is capable of in-

vading and destroying the anatomic relations in that region without giving a big palpable mass. But against that again is the absence of a long story of gall-bladder disease, because gallstones nearly always precede cholecystic carcinoma by twenty-five years or more.

As we go on in the story we find that the patient did begin to have epigastric pain and to vomit. It is also important to notice that the duodenal loop was not widened, because if we grant that there was a tumor well down in the ductal system it would not be surprising to find some abnormality by x-ray in that region. There is some flattening in the upper end of the duodenal loop, and I do not know whether to take that as evidence of an extrinsic mass. I assume that Dr. Schulz does not feel that way about it, and furthermore no mass was palpable. The stools were guaiac negative on many occasions, which is suggestive evidence at least that the patient did not have a tumor low in the ductal system, because the papilla of Vater tumor often gives a guaiac-positive stool when it ulcerates, even if it is only a tiny ulceration at the duodenal entrance of the duct. So, although his pain was minimal, I think the facts that the degree of obstruction fluctuated, that he had no palpable gall bladder and that he later had some epigastric discomfort and vomiting are in favor of obstruction due to stone. He had some weight loss, it is true; but I think we can and do see that in prolonged common-duct obstruction from any cause.

Dr. Chester M. Jones: I saw this man in consultation. In taking the history I got the story of an abrupt onset of gastrointestinal symptoms, followed about a week later by jaundice, anorexia and nausea. He was clear in telling the story to me, and he gave an excellent story of infectious hepatitis. The thing that was difficult for me to understand at the time was that he had had jaundice for many weeks without the slightest enlargement of the spleen, either then or subsequently. That to my mind is always a disturbing finding, because serious infection of the liver is frequently associated with moderate splenic enlargement. Even though one cannot feel the spleen it usually can be percussed or demonstrated by x-ray. The x-ray films gave no suggestion of enlargement of the spleen. When one cannot demonstrate that finding, the diagnosis of infectious hepatitis always should be treated with a good deal of reservation.

Dr. Moore: How about the normal temperature?

Dr. Jones: These patients usually have normal temperatures when jaundice sets in. Only a small proportion of them run a fever.

Our reasoning was similar to that of Dr. Moore, and we believed that the patient's disease was not running true to form, although for at least several weeks he really improved — the jaundice diminished, there was more bile in the stools, and it looked as if he were on the mend. Because he did not get beyond that point we thought that we had no right to postpone operation any longer. We decided on exploration. The family was told that he might have either carcinoma or gallstones.

Clinical Diagnosis

Choledocholithiasis?
Carcinoma of bile duct or pancreas?

Dr. Moore's Diagnosis

Choledocholithiasis.

Anatomical Diagnosis

Adenoacanthoma of pancreas.

Pathological Discussion

Dr. Benjamin Castleman: I am sorry that Dr. Arthur W. Allen is not here to describe the operation. At exploration he found a greatly distended gall bladder filled with bile. There were no stones in the gall bladder, and he could not feel any in the common duct. He did feel a large hard mass in the head of the pancreas, which was not definitely neoplastic or inflammatory. On the chance that it was a tumor, a cholecystostomy and jejunostomy were performed in preparation for a pancreatoduodenal resection to be done later. A biopsy was not taken because the lesion was too deep within the pancreas.

About three weeks later Dr. Allen resected the head of the pancreas and duodenum. At that time he noticed that the liver, which had been quite swollen and large at the first operation, had shrunken somewhat and that the mass in the pancreas seemed to be much larger than formerly; in fact, he was sure that the mass was a cancer. We did a frozen section and made a diagnosis of carcinoma. Unfortunately the tumor had spread into the body of the pancreas and was quite adherent to the portal vein, hepatic artery and superior mesenteric vein. Resection was carried through the body of the pancreas, but it was thought that all the tumor had not been removed. The carcinoma proved to be an adenoacanthoma, that is, an adenocarcinoma in which some of the epithelial cells had undergone squamous-cell change.

The patient did fairly well for a while but died four months following the operation. At autopsy we found that the tumor had extended down to the tail of the pancreas and that there were metastases in the liver, which were not present at the time of operation, and also in the lungs.

The patient died of cholemia and bronchopneumonia. He was extremely jaundiced. The tumor had invaded around the anastomosis, with ulcerations into the jejunum.

Dr. Moore: Had anyone ever felt a big distended gall bladder?

Dr. Jones: We tried again and again, but no one ever felt it.

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✱ INFECTIOUS HEPATITIS

Cases of epidemic jaundice and of homologous serum jaundice continue to attract a great deal of attention, large numbers still being encountered both in military practice and in the civilian population. Although deaths are relatively few, the disease is of considerable importance. Even in mild cases there is usually an acute illness that lasts about three or more weeks, and convalescence may be quite prolonged before there is a complete return to normal. Among American troops, particularly in cases that followed inoculation with yellow-fever vaccines containing the icterogenic agent, serious disabling sequelae of various sorts have been encountered. Interest in this subject therefore is great; intensive investigations have recently been made, and many are still in progress. Attention has already been called in these columns to some of the significant work that has contributed to an understanding of such conditions.[1, 2] A few of the more recent contributions have shed further light on this perplexing problem.

One of these studies is contained in a report to the Surgeon General of the United States Army by a special group of workers who investigated the cases of jaundice among Army personnel in the western region of the United States and their relation to vaccination against yellow fever.[3] Cases occurred in this area throughout 1942, but the main outbreak began in March and continued through July, with two peaks during that period. There had been a few small outbreaks of jaundice among civilians in California before the cases occurred in the Army, but the civilian cases could not have given rise to the widespread epidemics in the military personnel. It was more difficult, however, to determine whether some of the later cases in the Army might not have resulted from the earlier outbreaks.

In agreement with the results of many other workers, the jaundice in the Army personnel was traced to vaccination against yellow fever and particularly to a number of lots of vaccine, all of which contained the same human serum. The jaundice began in most cases from thirteen to sixteen weeks after the vaccination. Cases among unvaccinated individuals were scattered throughout the year, and in that respect they resembled the cases that occurred in men who were vaccinated with nonicterogenic lots of yellow-fever vaccine. The occurrence of such cases extended over a period of seventy-eight weeks after vaccination. The case fatality rate was 3 per 1000 among the patients with hepatitis who received the icterogenic lots of vaccine. It is of interest that, as a matter of chance, no icterogenic lots of vaccine had been used in foreign countries and in the Navy at the time of these investigations.

From their own studies these workers were not able to determine which of the various materials used in the preparation of yellow-fever vaccine actually contained the agent responsible for the outbreak of the post-vaccination jaundice. On the basis of the findings of others, however, they sus-

pected the human serums used in the preparation of the vaccines. Their suspicion was strengthened by the fact that all the icterogenic lots contained serum from donors who had previously suffered from catarrhal jaundice. It was thought that there was evidence to suggest that a fairly large proportion of normal persons act as carriers of the icterogenic agent, which they assumed to be a virus. They made numerous attempts to isolate the causative agent by inoculation of various experimental animals with the incriminated vaccines or with blood, tissues or excreta from jaundice patients. Their studies gave only negative or, at most, suggestive results.

A thorough pathological study based on 125 fatal cases of hepatitis that occurred in the United States Army during 1942 and made by Lieutenant Colonel Balduin Lucké,[4] of the Army Medical Museum, has recently been published. Many photographs of the gross and microscopical findings in the liver are shown, some of them in color. The findings were essentially those of yellow atrophy of the liver. The mechanism of the jaundice was considered to be obstruction of the lobular canaliculi. Cerebral lesions, consisting of an acute nonspecific degeneration of ganglion cells and a mild meningoencephalitis, were found in 5 per cent of the cases and were believed to be due to a loss of the detoxifying functions of the liver. The exact nature of either lesion, however, is not known.

In another paper, Lucké[5] presents the pathological findings in 14 patients who recovered from typical hepatitis during the epidemic and subsequently died or were operated on. In 6 of the cases death resulted from traumatic accidents, and 6 of the other deaths were due to unrelated diseases. In the 2 remaining cases a fragment of liver was removed in the course of an operation. The tissues were obtained from one to fourteen months after clinical recovery from the jaundice. In those who died from intercurrent diseases during convalescence or within a month after clinical recovery, the liver lobules were mostly reconstituted but there was still some evidence of the previous damage. In those examined more than one month after recovery, the liver parenchyma was completely restored without significant scarring and with only traces of the previous damage found in the portal areas; no evidence of permanent hepatic damage was found. It is well to mention, however, that these cases did not include any in which symptoms were prolonged for many months, as has been noted in some of the cases of post-inoculation jaundice. It is possible that in such cases considerable pathologic changes may persist.

Additional investigations concerning the etiology of these types of jaundice have also been recently reported. Neefe and his coworkers[6] succeeded in producing hepatitis in each one of 9 volunteers. In some of the subjects there were definite symptoms accompanied by jaundice, whereas in others there was demonstrable hepatitis by laboratory tests although clinical jaundice did not appear. In 5 of these subjects pooled mumps convalescent plasma was used; 4 of them developed hepatitis with jaundice, and the fifth showed laboratory evidence of mild hepatitis without jaundice. Two more received intravenous injections of plasma from one of the previous group twenty-five days after inoculation, and both developed mild hepatitis without jaundice; the donor of the plasma developed jaundice eighty-seven days after the plasma was obtained. Two more volunteers were given subcutaneous inoculations of a lot of yellow-fever vaccine known to be icterogenic, and both developed hepatitis, one with and the other without jaundice. One of the volunteers was reinoculated with the same material after recovery but remained free of disease during one hundred and forty days of observation. The onset of the disease in 6 of these 9 cases occurred twelve to thirty-five days after inoculation, which is a considerably shorter incubation period than that in most of the cases of post-vaccination or other types of homologous serum jaundice. There were 2 cases of jaundice that may have resulted from contact with one of the volunteers.

Some of the earlier studies of Findlay and his colleagues, particularly those concerned with the transmission of post-inoculation jaundice by means of intranasal inoculation, were referred to in a previous editorial.[2] More recently these workers[7] have reviewed the clinical findings in 689 cases of jaundice that occurred in the British Army. They have also presented immunologic and epidemiologic

observations purporting to show that post-vaccination jaundice, that is, homologous serum jaundice and infectious hepatitis or catarrhal jaundice, are caused by the same or closely related agents. This conclusion is based on three types of evidence. In the first place, they present case histories that suggest the spread of post-vaccination jaundice to contacts who had not been inoculated. Secondly, they ascertained the incidence of infectious hepatitis earlier in life among a sample of British officers and enlisted men and deduced from their findings that a previous attack of infectious hepatitis gave some, although not absolute, protection against post-inoculation jaundice. Finally, in complement-fixation tests with an antigen prepared from the liver of a patient who died of post-inoculation jaundice they obtained positive results with convalescent serums from patients with post-inoculation jaundice and also from patients with infectious hepatitis who had not been vaccinated. The complement-fixation test was not specific, however, giving positive results with serums from cases of arsenical hepatitis and yellow fever. The antigen responsible for the complement-fixation was not considered to be the agent responsible for the jaundice, since they obtained no positive takes following its inoculation. They also point out that hepatitis can occur without jaundice since positive complement-fixation tests were obtained in certain persons who gave no history of jaundice. They carried out additional transmission experiments, which, however, were mostly unsuccessful.

From a study of the answers to questionnaires among British officers and enlisted men these investigators obtained a history of catarrhal jaundice in 6.3 per cent of the 2614 men who replied. Only 4 men, or 2.6 per cent, of those with positive histories had a second attack, the period intervening ranging from one and a half to fifteen years. Among the 689 cases of hepatitis that they analyzed, relapses occurred in 14, or about 2 per cent, which is an incidence quite similar to that of those with a second attack of catarrhal jaundice.

A case reported by Neefe et al.[8] is of interest with respect to the relation of the two types of jaundice. Their case was one of a severe and prolonged hepatocellular jaundice following the injection of pooled mumps convalescent serum. This serum was given because of symptoms suggesting pancreatitis that developed in the course of an attack of mumps acquired by the patient from one of his children. The patient gave a history of having had a characteristic attack of catarrhal jaundice nine years previously. In this connection may be mentioned Hayman and Read's[9] report of an outbreak of 405 cases of jaundice following yellow-fever vaccination observed in an Army hospital between April and September, 1942. Among these cases were 7 in which a history was obtained of "catarrhal jaundice" occurring six months to twenty years previously. One patient stated that he had received yellow-fever vaccine in October, 1939, before going to South America for an oil company and that he developed jaundice in January, 1940, together with a number of other employees of the company. These authors subsequently observed another group of 100 cases of jaundice among troops returning from the combat zone who had had yellow-fever vaccine from twelve to eighteen months previously. Evidence of a short incubation period, suggesting that these were cases of epidemic jaundice or infectious hepatitis, was obtained from 2 cases in nurses. One of them had taken special care of a fatal case nineteen days before she developed jaundice, whereas the other had been "out" with an officer two days before he developed jaundice and became jaundiced after twenty-eight days.

Oliphant[10] attacked the problem more directly by inoculating icterogenic serum subcutaneously into persons convalescent from attacks of jaundice. He observed that recovery from homologous serum jaundice resulted in immunity to reinoculation with serum from acute cases of infectious hepatitis or with icterogenic yellow-fever vaccine. This immunity persisted for at least twelve to eighteen months. On the other hand, pooled serum obtained from one to three months after recovery from homologous serum jaundice, when mixed with icterogenic yellow-fever vaccine, failed to protect 1 of 10 persons who were inoculated with the mixture.

Havens and his co-workers[11] succeeded in transmitting hepatitis to 5 of 9 human volunteers in one institution by feeding specimens of serum, urine or

feces from both spontaneous and post-inoculation cases. The incubation period varied from twenty to eighty-four days, averaging thirty-seven. One case of moderately severe jaundice appeared among the uninoculated personnel of that institution fifty-one days after the beginning of the experiment and thirty-one days after the first experimental case had developed. At another institution 3 of 5 volunteers developed hepatitis from fifty to seventy days after the intracutaneous inoculation of icterogenic serum. In another series of feeding experiments the incubation period was found to be twenty-eight days,[12] which is considerably shorter than that after the inoculation of icterogenic serums.

The results of various transmission experiments are reviewed by MacCallum and others.[13] Transmission to pigs has been claimed by Danish workers, and the infection of chick embryos and canaries with materials from human cases has been reported by German investigators, but these results have not been confirmed. In man the disease has been produced by serum, duodenal juice, urine and feces from cases of infectious hepatitis and by serum and nasal washings from cases of homologous serum jaundice. It is also claimed that the jaundice resulting from arsenotherapy may result from traces of serum left in the syringe from previous injections of other patients who harbored the infectious agent. The latter possibility is rendered plausible by the experience of Bradley et al.,[14] who observed an outbreak of homologous serum jaundice involving 57 per cent of persons injected with a particular batch of pooled human serum that was being used in a study of allergic reactions. Jaundice resulted from doses varying from 0.1 to 1200 cc. Neither the incubation period, which varied from forty-five to one hundred and four days, nor the severity of the jaundice was related to the size of the dose.

All these observations are of considerable interest, but many important problems still remain unsolved. It is to be expected that current investigations will shed further light on the etiologic agent and on many of the clinical features of this disease. In the meantime it is obvious that one is dealing with a serious infection caused by a fairly sturdy agent, which is transmissible through inoculation, as well as through natural channels, and which may persist for considerable periods in the patient. The most obvious implication is that blood banks should refuse to accept as donors persons who have had an attack of infective hepatitis within a few months — possibly within a year. To obtain more information concerning the occurrence and spread of this important disease it is also imperative that it be made reportable. Such facts could then be applied to the control and prevention of the disease. In this connection, the possible value of gamma globulin in the prevention and modification of the disease is now under investigation.

References

1. Editorial. Jaundice from human serum. *New Eng. J. Med.* **229**:91, 1943.
2. Editorial. Epidemic jaundice. *New Eng. J. Med.* **230**:297-299, 1944.
3. Sawyer, W. A., Meyer, K. F., Eaton, M. D., Bauer, J. H., Putnam, P., and Schwentker, F. F. Jaundice in army personnel in western region of United States and its relation to vaccination against yellow fever. *Am. J. Hyg.* **39**:337-430 and **40**:35-107, 1944.
4. Lucké, B. I. Pathology of fatal epidemic hepatitis. *Am. J. Path.* **20**:471-593, 1944.
5. *Idem.* II. Structure of liver after recovery from epidemic hepatitis. *Am. J. Path.* **20**:595-619, 1944.
6. Neefe, J. R., Stokes, J., Jr., Reinhold, J. G., and Lukens, F. D. W. Hepatitis due to injection of homologous blood products in human volunteers. *J. Clin. Investigation* **23**:836-855, 1944.
7. Findlay, G. M., Martin, N. H., and Mitchell, J. B. Hepatitis after yellow fever inoculation: relation to infective hepatitis. I. Clinical and pathological findings. *Lancet* **2**:301-307 and 340-344, 1944. II. Immunology and epidemiology. *Ibid.* **2**:365-370, 1944.
8. Neefe, J. R., Miller, T. G., and Chornock, F. W. Homologous serum jaundice: review of literature and report of case. *Am. J. M. Sc.* **207**:628-638, 1944.
9. Hayman, J. M., Jr., and Read, W. A. Some clinical observations of outbreak of jaundice following yellow fever vaccination. *Am. J. M. Sc.* **209**:281-296, 1945.
10. Oliphant, J. W. Infectious hepatitis: experimental study of immunity. *Pub. Health Rep.* **59**:1614-1616, 1944.
11. Havens, W. P., Jr., et al. Experimental production of hepatitis by feeding icterogenic materials. *Proc. Soc. Exper. Biol. & Med.* **57**: 206-208, 1944.
12. Havens, W. P., Jr., et al. Human transmission of infective hepatitis by oral route. *Lancet* **1**:202, 1945.
13. MacCallum, F. O., et al. Discussion on infective hepatitis, homologous serum hepatitis and arsenotherapy jaundice. *Proc. Roy. Soc. Med.* **37**:449-460, 1944.
14. Bradley, W. H., Loutit, J. F., and Maunsell, K. Episode of "homologous serum jaundice." *Brit. M. J.* **2**:268, 1944.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHESBRO — Lt. Comdr. Wallace L. Chesbro, formerly of Springfield, was killed on April 28 when the hospital ship, *U. S. S. Comfort*, was attacked by a Japanese suicide pilot off the coast of Okinawa. He was in his thirty-third year.

Dr. Chesbro received his degree from Tufts College Medical School in 1938. He was a fellow of the American Medical Association.

His widow, his daughter, his mother and two brothers survive.

HAVILAND — Walter C. Haviland, M.D., of Mansfield Depot, Connecticut, died May 14. He was in his sixty-fourth year.

Dr. Haviland received his degree from Baltimore Medical College shortly before he moved to Worcester in 1904. He became superintendent of the Herbert Hall Hospital in 1912, and on May 10, 1932, was appointed to the Worcester Board of Health. In 1934 he left Worcester to take a position at

the Connecticut State Hospital at Middletown, where he stayed five years before going to Mansfield in 1939. He was a member of the American Society of Psychiatrists and the Connecticut State Medical Society and a fellow of the American Medical Association.

His widow, a daughter and three grandchildren survive.

HIRSCH — Henry L. Hirsch, M.D., of Springfield, died May 8. He was in his sixty-first year.

Dr. Hirsch received his degree from Jefferson Medical College in 1906. He served on the Springfield School Committee from 1913 to 1920. He was a first lieutenant in the United States Army during World War I. He was a fellow of the American Medical Association.

His widow, two brothers and three sisters survive.

MAKLER — Mark Makler, M.D., of Lynn, died May 14. He was in his forty-third year.

Dr. Makler received his degree from Northwestern University Medical School, Chicago, in 1927. He was a member of the staffs of the Children's Hospital, Boston, and of the Lynn Hospital. He was a member of the New England Pediatric Society and a fellow of the American Medical Association.

His widow, two sons, his mother and a sister survive.

MOORE — John H. Moore, M.D., of Boston, died February 24. He was in his seventy-sixth year.

Dr. Moore received his degree from Harvard Medical School in 1897. For many years he was medical examiner for the John Hancock Mutual Life Insurance Company.

THISSELL — J. Abbott Thissell, M.D., formerly of Beverly, died May 14. He was in his eighty-seventh year.

Dr. Thissell received his degree from Harvard Medical School in 1885. He was formerly a member of the Massachusetts Medical Society.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Lowell	June 1	Albert H. Brewster
Salem	June 4	Paul W. Hugenberger
Haverhill	June 6	William T. Green
Brockton	June 14	George W. Van Gorder
Worcester	June 15	John W. O'Meara
Pittsfield	June 18	Frank A. Slowick
Springfield	June 20	Garry deN. Hough, Jr.
Fall River	June 25	Eugene A. McCarthy
Hyannis	June 26	Paul D. Norton

MISCELLANY

NOTE

A new medical society, the New Hampshire Roentgen-Ray Society, was founded a few months ago. The aims of the society are to maintain and improve the standards of x-ray service in that state. Dr. Fred S. Eveleth of Concord was elected president, and Dr. Richard C. Batt, of Berlin, secretary.

CORRESPONDENCE

RH FACTOR

To the Editor: The editorial "The Rh Blood Factor" in the April 19 issue of the *Journal* is timely and brings attention to a subject to which physicians as a whole are giving scant regard. Strangely enough, even in Boston, where the Blood Grouping Laboratory directed by Dr. Louis K. Diamond has been most active, most physicians view this subject as being of no practical importance. The editorial, however, in its attempt to emphasize the practical importance of this subject has possibly conveyed a wrong impression, which I believe was not intended.

In one paragraph the editorial reads, "The practical importance of the Rh factor concerns Rh− women and their Rh+ offsprings." May I disagree that the practical importance of this factor is in pregnancy alone, which is implied in the above quotation. The practical importance of the Rh factor concerns all Rh− people, whether it be man or woman.

To quote further from the editorial: "The inferences are obvious. Rh− persons should not receive repeated transfusions from Rh+ donors." The foregoing statement leads to an erroneous conclusion because of the word "repeated." It implies that one transfusion of Rh+ blood to an Rh− person is of no consequence. Again, the editorial would be much more accurate if it were written, "Rh− persons should not receive any whole-blood transfusions from Rh+ donors." For instance, a young girl long before she enters the stage of puberty may have to receive a whole-blood transfusion for one reason or another. If she is Rh− and is transfused with Rh+ blood and then years later is married to an Rh+ man and becomes pregnant, her first pregnancy may be seriously affected by the transfusion given years before. In other words, such a transfusion sets a stage that years later may seriously affect her and her offspring's health and viability. On the other hand, if an Rh− man or boy, for one reason or another, is given a transfusion of Rh+ blood, that individual may be sensitized for the remainder of his life. At a much later date he may be involved in a serious accident or may have to undergo a major operation in a hospital, either of which may demand an immediate whole-blood transfusion. If in this emergency procedure he is again given Rh+ blood, — and he has an 87 per cent chance of this being so, — he is likely to suffer a transfusion reaction, which may kill him or at best will add insult to injury. Therefore, it is important in every case that an Rh− man, woman or child does not receive Rh+ blood.

I realize that the editorial later explains the phrases and words quoted above, but my point is that most people, if they peruse the editorial page, read the first sentence of a paragraph or at least remember only that part of it and may not read the subsequent sentences and paragraphs.

I believe that calling attention to these statements about whole-blood transfusions will impress your readers to the extent of encouraging changes in their methods and ideas of testing blood prior to transfusion.

William Freeman, M.D.

Worcester State Hospital
Worcester, Massachusetts

NOTICES

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, June 7, at 7:15 p.m. in the classroom of the nurses' residence. Mr. Lester W. Dearborn will speak on the subject "Some Psychological Aspects of Frigidity." Dr. Lucile Lord-Heinstein will be chairman.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, June 7

Friday, June 8

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building. Boston City Hospital.

12:00 m.–1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

Saturday, June 9

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(*Notices continued on page xix*)

NOTICES (*Continued from page 664*)

MONDAY, June 11
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.
TUESDAY, JUNE 12
*9:00–10:00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
WEDNESDAY, JUNE 13
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

JUNE 7. New England Hospital for Women and Children. **Page 664.**

JUNE 14–19. American Board of Obstetrics and Gynecology. **Page 364, issue of March 22.**

JUNE 16. American College of Chest Physicians. **Page xvii, issue of May 10.**

SEPTEMBER 17. American Public Health Association. **Page 752, issue of November 30.**

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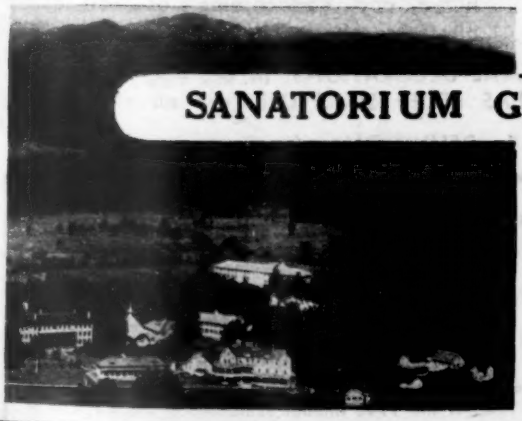

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1. **SUBJECT:** "Courage and Devotion Beyond the Call of Duty" — on the part of members of the medical profession — in military or civilian practice. Any contestant may portray either the military or civilian aspect of the subject (or both, if shown in one piece).

2. **MEDIA:** The physician-artist's choice of one of the following:

   1. PAINTING in oil or egg tempera.
   2. WATER COLOR, transparent or opaque.
   3. SCULPTURE in any medium.
   4. DRAWING in any medium.
   5. PRINTS, including etching, engraving, lithography, wood block and linoleum block (on paper or cloth).
   6. PHOTOGRAPHY, including bromoil, tinted and Kodachrome, as well as photo-montage.

   SUGGESTIONS: COMPLETE SKETCHES FOR MURAL DECORATIONS: In oil, egg tempera or water color drawing; PHOTO MURAL; BAS RELIEF SCULPTURE: are all eligible.

3. **ELIGIBILITY** — See Footnote ★

4. **DEFINITION** — See Footnote ★

5. **PRIZES: Forty-two prizes, divided amongst the two groups of physicians:**

To medical officers:	To civilian physicians:
1 $2,000 War Bond (E or F series)	1 $2,000 War Bond (E or F series)
10 $1,000 War Bonds (E or F series)	10 $1,000 War Bonds (E or F series)
10 $ 500 War Bonds (E or F series)	10 $ 500 War Bonds (E or F series)

No physician may submit more than one piece nor win more than one of the 42 prizes. No physician is eligible for a prize unless he also submits for exhibition at either the 1945 or the 1946 annual exhibition of the A.P.A.A. at least one other original work (not previously exhibited at an A.P.A.A. Exhibition) in any medium, on any subject of his own choice. Prizes will be awarded on a basis of conception and execution, irrespective of medium employed.

6. **JUDGES** — See Footnote ★

7. **EXPIRATION DATE** — See Footnote ★

8. **PURPOSE OF THE COMPETITION:** To memorialize the heroism and devotion of the medical profession in war and peace. All exhibitors (including prize-winners) shall retain ownership of their pieces. It is understood, however, that the A.P.A.A. shall have reproduction rights and also the privilege, for a period of three years after the close of the contest, of displaying prize-winning objects, at art museums, libraries, county medical societies, medical schools, hospitals, and similar institutions for the purpose of enhancing the public's estimate of the medical profession. The Association shall also have the right to offer institutions such as those mentioned above, the privilege of copying any of the prize-winning objects for use as murals, cornerstones, friezes, architectural designs, etc. — for the purpose of memorializing the medical profession's importance in war and in peace.

★ **FURTHER INFORMATION** available on request of the Association's Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Cal., or Mead Johnson & Co., Evansville 21, Ind., U.S.A.